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THE USE OF A SYNTHETIC BRONCHODILATING AGENT (ISOPROTERENOL SULFATE) IN THE TREATMENT OF BRONCHIAL ASTHMA IN CHILDREN

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THE practical and significant aspect of this study was to evaluate the effectiveness of a formulation* containing isoproterenol sulfate in a syrup form for oral use in children afflicted with clinical symptoms of asthma or allergic bronchitis. Heretofore, the available forms of isoproterenol which had to be administered as tablets, sublingual glossets, or aerosols in solution or in powder form for inhalation by nebulizers, have posed special problems of administration in small children under five years of age. The study was made between September 1959 and May 1960.

EXPERIMENTAL PROCEDURE

Method of Study.—The effectiveness of the formulation was compared with that of a placebo identical in appearance and taste, used for the relief of coughing and wheezing in patients with asthma or allergic bronchitis. The study was double-blind and neither the parent nor the attending physician knew which syrup was prescribed.

Both syrups were tested on each patient, so that each patient could serve as his own control. Our plan was that half of the patients should receive

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*Supplied as Norisodrine® syrup by Abbott Laboratories, North Chicago, Illinois. Each teaspoon contains: isoproterenol sulfate—3 mg., calcium iodide (anhydrous)—150 mg., alcohol—6 per cent, in a honey-mint flavored syrup.

TABLE I. TABULATION OF INDIVIDUAL CASE DATA

Patient	Test Order	Cough				Wheeze			
		Test Period Isoproterenol		Test Period Placebo		Test Period Isoproterenol		Test Period Placebo	
		Incidence of Symptom	Incidence of Symptom Relief	Incidence of Symptom	Incidence of Symptom Relief	Incidence of Symptom	Incidence of Symptom Relief	Incidence of Symptom	Incidence of Symptom Relief
1	P.I.*	1	1	1	1	1	1	1	1
2	P.I.	28	27	26	13	16	9	18	5
3	I.P.	11	11	9	9	2	0	1	0
4			I.D.*				I.D.		
5	I.P.	4	2	1	1		I.D.		
6	P.I.	14	7	18	18		I.D.		
7	P.I.	11	10	24	22	3	0	14	7
8	I.P.	5	0	9	0	5	0	9	1
9	I.P.	3	3	3	2		I.D.		
10	P.I.	4	4	3	3	1	1	2	1
11	I.P.	1	1	5	5	2	0	7	0
12			I.D.				I.D.		
13	I.P.	27	27	26	21	29	29	26	21
14, 15, 16			I.D.				I.D.		
17	I.P.	16	8	13	0	26	17	13	0
18	P.I.	17	16	5	4		I.D.		
19			I.D.				I.D.		
20	P.I.	5	3	2	1	5	3	2	1
21	I.P.	6	6	12	12	1	1	2	1
22			I.D.				I.D.		
23	I.P.	20	18	17	17	20	18	16	10
24	I.P.	10	8	9	3	2	2	5	2
Totals		183	146	183	132	113	81	116	50

*P=Placebo
I=Isoproterenol
I.D.=Insufficient data

the test drug first, followed by the placebo. The other half was scheduled to receive the placebo first.

The parents were given a record form and were asked to record the date each dose was given, whether it was given for cough or wheeze (or for both) and whether the symptom was relieved. Unusual symptoms following medication were to be noted and recorded. The record forms were collected at each visit.

The standard prescription was given as needed at intervals, and dosage was based on the following recommendations:

1-3 years	½ teaspoon. Repeated in two hours if necessary
3-10 years	½-1 teaspoon. Repeated every thirty minutes up to a total of 3 teaspoons
10 years and over	1-2 teaspoons, with additional teaspoons given according to tolerance

Description of Sample.—The patients were from two sources: Children attending the allergy clinic at the District of Columbia General Hospital and children from the private practice of a pediatric allergist. All patients had the diagnosis of bronchial asthma or allergic bronchitis. Clinical manifestations varied from mild to severe.

Only seventeen of the twenty-four patients studied were treated for cough during both the medicinal agent and placebo test periods. These seventeen cases constitute our "cough" group. Only thirteen of the twenty-four patients

were treated for wheezing during both test periods. These thirteen cases constitute our "wheeze" group. All thirteen cases in the "wheeze" group are included also in the "cough" group. Isoproterenol was tested first on ten of the seventeen patients in the "cough" group and on eight of the thirteen in the "wheeze" group.

TABLE II. DISTRIBUTION OF CASES BY SYMPTOM FREQUENCY BY TEST PERIOD AND BY TEST ORDER

	Cough Group		Wheeze Group	
	No. Cases	Symptom Incidence Per Case	No. Cases	Symptom Incidence Per Case
Isoproterenol test period	2	1	3	1
	7	2-10	6	2-10
	6	11-26	3	11-26
	2	27-28	1	27-29
	17	Range=1-28	13	Range=1-29
Placebo test period	2	1	2	1
	8	2-10	6	2-10
	5	11-25	4	11-25
	2	26	1	26
	17	Range=1-26	13	Range=1-26
	No. Cases	Test Order	No. Cases	Test Order
	10	Isoproterenol-Placebo	8	Isoproterenol-Placebo
	7	Placebo-Isoproterenol	5	Placebo-Isoproterenol
	17		13	

Method of Analysis.—The data from the parents' record forms were tabulated in terms of two symptom groups, (cough and wheeze) and two test periods (isoproterenol and placebo). This tabulation by case number, of symptom incidence and symptom relief incidence, is shown in Table I. Only those patients who were treated for the respective symptoms during both test periods were included in the respective symptom groups for further analysis. Excluded cases are indicated by the entry "I.D." Column 2 indicates the order of the two test periods for each case.

The distribution of included cases by symptom frequency per test period is summarized in the upper part of Table II. The lower part of the same table shows the distribution of cases by test-period order for the two symptom groups. It was apparent by inspection that the symptom-incidence per test period for individuals was too low and too variable to support a statistical estimate of the proportion of individuals whose symptoms would respond significantly better to isoproterenol than to the placebo.

Group symptom-incidence per test period, however, was great enough to warrant statistical comparison of group response to isoproterenol with group response to the placebo. This comparison was made for both symptom groups. Group incidence of relief was converted to a percentage of group incidence of the symptom, for each test period. Then the difference between the two percentages was divided by the standard error of the difference, to

TABLE III. COMPARISON OF THE EFFECTIVENESS OF ISOPROTERENOL SYRUP WITH THAT OF PLACEBO IN EACH SYMPTOM GROUP

Sample	Number of Cases	Total Incidence of Symptom	Range of Incidence Per Case	Mean Incidence Per Case	Total Incidence of Relief	Per Cent Relief	Comparison of Per Cent Relief
Cough group							
Isoproterenol test period	17	183	1-28	10.77	146	79.78	% difference 7.65
Placebo test period	17	183	1-26	10.77	132	72.13	CR=0.17 (not significant)
Wheeze group							
Isoproterenol test period	13	113	1-29	8.69	81	71.68	% difference 28.58
Placebo test period	13	116	1-26	8.92	50	43.10	CR=4.37 <.01 (significant)

obtain the critical ratio. Finally, the critical ratio was referred to a standard table to determine its significance. The results are shown in Table III.

RESULTS

The total symptom incidence for the "cough" group in both the medicinal and placebo test periods was 183. The total symptom incidence for the "wheeze" group was 113 for the isoproterenol test period and 116 for the placebo test period (See Tables I and III).

The distribution of symptom incidence per case is summarized in Table II for both the "cough" and "wheeze" groups by test periods and by test order. It is apparent from Table II that our data cannot support any conclusions regarding the percentage of cases helped. Therefore, the following discussion refers to group statistics only, which are presented in Table III.

In the "cough" group, symptom relief was 79.78 per cent with the isoproterenol and 72.13 per cent with the placebo. No significant difference was observed between the medicinal agent and the placebo in relieving cough.

In the "wheeze" group, symptom relief was 71.68 per cent with isoproterenol and only 43.10 per cent with placebo. The difference in relief between the drug and placebo was 28.58 per cent. The critical ratio was 4.37, which is significant at better than the 1 per cent level of confidence. The drug was significantly more effective in relieving the symptom of wheezing than was the placebo.

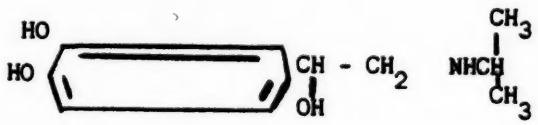
Only one patient (in the "cough" group) reported the occurrence of headache and abdominal pain following the administration of a prescribed dosage of the drug. There was no recurrence of these symptoms after the dosage was reduced.

DISCUSSION

The symptomatology of bronchial asthma in children is characterized essentially by coughing, wheezing, and dyspnea. Clinically, individual attacks vary in severity from mild to severe and may last from a few minutes to

several days in duration. The pathophysiology is generally believed to depend on local irritation of the bronchial mucous membranes and varying degrees of bronchial obstruction resulting from a combination of factors such as local edema, spasm and mucus accumulation.

Isoproterenol sulfate is a synthetic amine having sympathomimetic properties. It is chemically related to epinephrine and ephedrine. Its structural formula is:



The drug has been variously designated under such names as Norisodrine® (Abbott), Isuprel® (Winthrop-Stearns), aludrine, isopropyl epinephrine, and others.

Segal, Beakey and Bresnick were the first investigators to report the successful use of Isuprel aerosol in the treatment of bronchial asthma in adults.[1,2] Lowell, Curry and Schiller subsequently found the drug of value as an aerosol in the treatment of mild or moderately severe asthma.[3] When the drug was employed as a sublingual tablet, they observed no side reactions other than a bitter taste in fifteen adult asthmatic patients. Gay and Long administered the drug to patients who ranged in age from fifteen to seventy-five years.[4] They gave the drug sublingually, orally, subcutaneously and by inhalation. Oral medication was prescribed in capsule form in doses of 15 mg. to 50 mg. They observed wide variations in both therapeutic response and incidence of side reactions among patients. They found that the routine use of the drug by mouth was impractical because of the high incidence of side effects (75 per cent). Untoward symptoms may consist of dizziness, headache, palpitation, nervousness, tachycardia, weakness, tremors, nausea, sweating, and the like.

The effectiveness of isoproterenol in relieving the wheeze of bronchial asthma is attributable to its bronchiole-dilating effect and also to its tendency to liquefy bronchial secretions.[4] Gay and Long, confirming the observations of Segal and his co-workers,[1,2] found that this drug was most effective in the treatment of bronchial asthma in their patients (ages fifteen to seventy-five years) when administered by inhalation in a nebulized mist. Unfortunately, this method is not readily applicable to young children. The drug is readily absorbed following oral administration. Prolonged use is said to be well tolerated.[5] The formulation (syrup) employed in our study was taken well by the children. Relief usually appeared within thirty minutes after medication and lasted one to three hours in mild or moderate attacks.

CONCLUSIONS

A medicinal formulation (syrup) containing isoproterenol was evaluated by means of a double-blind study for its effect in controlling coughing and wheezing in children with bronchial asthma or allergic bronchitis following oral administration.

The drug and the placebo were about equally effective in controlling cough. However, the drug was significantly more effective than the placebo in relieving the symptom of wheezing.

The drug was accepted well by the children. Only one child exhibited untoward reaction (headache and abdominal pain) after administration of the medication. These symptoms disappeared when the dosage was decreased.

This formulation has the advantage of being in a palatable syrup which can be easily administered to small children.

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ON THE NOTION OF CAUSE

To sum up: The strict, certain, universal law of causation which philosophers advocate is an ideal, possibly true, but not *known* to be true in virtue of any available evidence. What is actually known, as a matter of empirical science, is that certain constant relations are observed to hold between the members of a group of events at certain times, and that when such relations fail, as they sometimes do, it is usually possible to discover a new, more constant relation by enlarging the group. Any such constant relation between events of specified kinds with given intervals of time between them is a "causal law." But all known causal laws are liable to exceptions, or at least are not known to have no exceptions: we believe, on the basis of a good deal of experience, that such exceptions can be dealt with by enlarging the group we call the cause, but this belief, wherever it is still unverified, ought not to be regarded as certain, but only as suggesting a direction for further inquiry.—BERTRAND RUSSELL—From *Our Knowledge of the External World*, a Mentor Book, published by the New American Library, New York, 1960.

MOLDS AND BACTERIA IN THE ETIOLOGY OF RESPIRATORY ALLERGIC DISEASES

XXI. Studies with Mold Extracts Produced from Cultures Grown in Modified Synthetic Media

A Preliminary Report

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AS EARLY AS 1942, the diagnostic value of conventional mold extracts had been questioned.[1] Since that time, the major effort of The Association of Allergists for Mycological Investigations has been directed to improvement in mold allergen extraction. Investigations have included comparisons of extracts prepared from pellicles by various modifications, and from culture broth fractions.

REVIEW OF TECHNIQUES

We have evaluated mold extracts, identified by series numbers in earlier publications,[3,4,7] from the following sources:

1. Washed pellicles, dried by lyophilization
2. Washed pellicles, dried by lyophilization, defatted
3. Washed pellicles, dried by lyophilization, defatted, ground
4. Washed pellicles, dried by lyophilization, ground
5. Washed pellicles, air-dried (usual method)
6. Unwashed pellicles, dried by lyophilization
7. Unwashed pellicles, dried by lyophilization, defatted
8. Culture broth
9. Dialysate of aqueous extracts of unwashed pellicles
10. Dialyzed aqueous extracts of unwashed pellicles
11. Dialysate of culture broth
12. Dialyzed culture broth

13-32. Precipitates by various concentrations of acetone

33. Precipitates by 90 per cent volume concentration of acetone

The clinical studies with mold allergen preparations 1-12 revealed three facts: (1) No simple pellicle extract prepared by any of the modifications is superior to extract prepared by our earlier or usual method. (2) The culture broth affords the highest source of allergen content. (3) Mold allergen fractions are essentially non-dialyzable. With extracts 13-32 it was found that all precipitates after treatment with various concentrations between 50 and 93 per cent by volume of cold acetone were allergenic.

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Type 33 extract is prepared from all precipitate following a single treatment with an excess, 90 per cent by volume, of cold acetone. The preliminary aqueous extract is, however, dialyzed as suggested by studies with extracts 10 and 12. Furthermore, to utilize its greater allergen content, as found in studies with extract 8, culture broth ordinarily is employed for the preliminary aqueous extract. Finally, accurate standardization of the finished extract on the weight-volume basis is accomplished from the lyophilized solution of redissolved precipitate.

In previous publications[2,3,5,6] we have supported the superiority of Type 33 mold allergens. We have made no particular claims for increased purity of these extracts, but we have felt that they are so highly concentrated that they react specifically in dilutions at which non-specific reactions usually do not occur. However, we have never been completely satisfied with Type 33 preparations, because of the difficulty in freeing them entirely of culture medium by either dialysis or acetone precipitation.

As early as 1939 we had found no natural or synthetic medium which compared favorably with malt extract broth* with which we have consistently obtained typical and vigorous mold growth satisfactory for allergen extract preparation. We have explored many variations in culture techniques, including the use of mechanical devices in systems designed to accomplish dialysis of the culture broth simultaneously with the growth period. Our first encouragement in culture technique improvement occurred some years ago with modified synthetic media when we fortified Czapek's formula with "building blocks" in the form of varying amounts of natural substances. We were impressed that the addition of surprisingly small amounts of natural nutrients to synthetic media containing otherwise only ingredients of known chemical composition afforded markedly superior and more characteristic growth than we observed with any purely synthetic medium.

Following further studies over the past three years with various combinations of salts in fortified synthetic media, we have developed culture media for the preparation of allergenic mold extracts from which the final traces of the media may be removed by dialysis. With these modified synthetic media we have obtained very satisfactory growth of all the molds in our list with abundant sporulation at maturity.

MMP EXTRACTS

We have selected one of these media for preparation of the extracts herein discussed.

In the preparation of these extracts, the culture broth is successively separated mechanically from the mature pellicle, concentrated by evaporation, dialyzed for complete removal of unutilized nutrients, and dried by lyophilization. The dried material is dissolved on an arbitrary weight-volume basis in an appropriate extracting fluid, and the resulting extract is

*The Difco Company, Detroit, Michigan.

TABLE I. TEN MMP EXTRACTS

Extract	Acetone-Precipitated	Not Acetone-Precipitated	PNU	Weight/Volume
Alternaria tenuis MMP-1	−	+	44,000	1:50
Alternaria tenuis MMP-3-A	−	+	65,000	1:50
Alternaria tenuis MMP-3-B	+	−	65,000	1:50
Curvularia specifera MMP-278-1	−	+	70,000	1:50
Curvularia specifera MMP-278-2	+	−	90,000	1:50
Spondylocladium sp. MMP-276	−	+	122,000	1:50
Helminthosporium interseminatum MMP-277-1	−	+	45,000	1:50
Helminthosporium interseminatum MMP-277-2	+	−	88,000	1:50
Hormodendrum cladosporioides MMP-2	−	+	26,000	1:50
Stemphylium botryosum MMP-275	−	+	35,000	1:50

sterilized by passage through a bacterial filter. Allergen solutions prepared in this way are known as MMP extracts.

If acetone precipitation is to be employed, it can be accomplished by adding 90 per cent by volume of cold acetone to the concentrated and dialyzed broth, after which the precipitate is redissolved and dialyzed for removal of the acetone. From this point, the procedure is the same as for non-precipitated extracts.

In late 1959, ten MMP extracts* were prepared and distributed to members collaborating in these studies (Table I). Seven of these extracts were prepared in the usual manner: without acetone precipitation; the additional step of acetone precipitation was employed for the other three. Alternaria extracts MMP-3-A and MMP-3-B were prepared respectively by regular and acetone precipitation techniques from a single lot of broth which had been divided into two equal portions after dialysis.

CLINICAL STUDIES

Selection of Patients.—An effort was made to employ the MMP extracts for tests on patients sensitive to the respective molds, as well as on normal persons, or on allergic patients not sensitive to the molds being studied. The diagnosis of mold sensitivity had, in most instances, been made by prior tests with other extracts. The number of sensitive and non-sensitive patients reported for each mold by the investigators may be seen in Table II.

Skin Tests.—Skin tests were made by both scratch (prick or punch) technique with the 1:50 concentrates, and by intradermal titrations with dilutions of 1:1,000 to 1:100,000, or occasionally with greater dilutions. Most patients received both scratch and intradermal tests, although a few patients received only one or the other. Non-sensitive patients, ordinarily, were tested only with the 1:1,000 dilution intradermally after they had reacted negatively on the initial scratch tests.

Results of Skin Tests.—In our studies on sensitive patients, we were impressed with the diagnostic efficiency in scratch tests, and in intradermal

*Prepared and supplied, in part, by the Hollister-Stier Laboratories, Spokane, Washington.

TABLE II. CLASSIFICATION OF PATIENTS

Investigator	*Alternaria*		*Curvularia*		*Spondylocladium*		*Helminthosporium*		*Hormodendrum*		*Stemphylium*	
	A	B	A	B	A	B	A	B	A	B	A	B
Halpin	8	3	2	9	5	6	4	7	3	8	7	4
Talbott	6	13	5	14	3	16	4	15	7	12	5	14
Bartlett	8	6	3	11	1	13	4	10	8	6	6	8
Prince	16	18	15	19	15	17	15	19	11	23	16	18
Etter-Raymer-Jackson	6	8	6	8	6	8	6	8	6	8	6	8
Mansmann	2	6	2	6	2	6	—	—	2	6	2	6
Eisenberg	6	5	6	5	6	5	6	5	6	5	6	5
Frayser	3	10	3	10	3	10	3	10	3	10	3	10
Sensitive	55		42		41		42		46		51	
Not sensitive		69		82		81		74		78		72
Totals	124		124		122		116		124		123	

A—Sensitive.
B—Not sensitive.

TABLE III. REACTIONS IN SENSITIVE AND NON-SENSITIVE PATIENTS

Extract	Punch 1:50 (Scratch)		Intradermal					
			1:100,000		1:10,000		1:1000	
	Patients	Per Cent	Patients	Per Cent	Patients	Per Cent	Patients	Per Cent
Alternaria MMP-1	53*	88	41	85	20	80	9	100
PNU:44,000 (1:50)	54**	2	22	0	23	26	56	18
Curvularia MMP-278-1	40	85	31	84	18	94	5	100
PNU: 70,000 (1:50)	65	3	35	3	32	22	67	15
Curvularia MMP-278-2 Acetone precipitated	37	86	30	80	15	93	7	100
PNU: 90,000 (1:50)	64	3	34	6	32	19	65	14
Spondylocladium MMP-276	39	82	30	83	18	89	6	100
PNU: 122,000 (1:50)	63	3	35	0	32	13	63	11
Helminthosporium MMP-277-1	42	80	31	84	17	100	5	100
PNU: 45,000 (1:50)	60	0	26	0	23	21	56	16
Helminthosporium MMP-277-2 Acetone precipitated	42	79	31	84	16	100	5	100
PNU: 88,000 (1:50)	59	2	31	3	29	17	62	21
Hormodendrum MMP-2	43	40	33	54	27	85	18	94
PNU: 26,000 (1:50)	60	2	29	0	25	4	57	16
Stemphylium MMP-275	50	90	41	90	14	86	4	75
PNU: 35,000 (1:50)	53	2	25	0	23	21	57	12

*Upper figures in each "Extract" category reflect number of patients, and percentage of diagnostic reactions in sensitive patients.
**Lower figures reflect number of non-sensitive patients, and percentage of positive reactions.

TABLE IV. INTRADERMAL SKIN TEST TITRATIONS

Alternaria MMP-3-A Non-Precipitated (Regular) Extract	No. of Patients	Alternaria MMP-3-B Acetone Precipitated Extract	No. of Patients
Reacted at:		Reacted at:	
1:10 million or higher dilutions	10	1:10 million or higher dilutions	8
1:1 million	2	1:1 million	7
Greater concentration than 1:1 million	3		
Total	15		15

tests with the higher dilutions, of all the allergens except Hormodendrum (Table III). In relatively few instances was it necessary, and frequently it was not considered safe, to continue intradermal titrations to the 1:1,000 concentration. At this strength, the diagnostic efficiency of the extracts in intradermal tests was uniformly high (Stemphylium was tested in too few patients to be of significance). One patient had a systemic reaction after intradermal tests with Alternaria and the two Curvularia extracts applied simultaneously in dilutions of 1:100,000; this patient had received no other test injections. Another patient reacted to each of the Helminthosporium extracts and to the Stemphylium extract in dilutions of 1:1,000,000. The MMP extracts were singularly free of irritative properties in scratch tests and in intradermal tests in the higher dilutions.

Acetone Precipitation.—Two of the acetone-precipitated extracts (Curvularia MMP-278-2 and Helminthosporium MMP-277-2) were included for comparative tests with non-precipitated extracts of the same species, and with non-precipitated extracts of four other dematiaceous molds. No significant differences were noted in reactivity to either scratch or intradermal tests with the acetone-precipitated extracts and their respective non-precipitated counterparts. Furthermore, the reaction patterns were essentially the same for the acetone-precipitated extracts and the non-precipitated extracts of the other dematiaceous molds (Table III).

The two Alternaria extracts prepared from the same broth (one by acetone precipitation, the other by the usual technique) were compared by scratch tests and by intradermal titrations on fifteen sensitive patients (Tables IV and V). No significant differences were noted between the two extracts in these tests.

Concentration of Extract for Scratch Testing.—Our initial scratch (punch or prick) tests were performed with concentrated (1:50) glycero-saline solutions. After earlier studies had revealed the unusual potency of the MMP extracts, we performed scratch tests with other concentrations of Alternaria extract on seventeen patients who had reacted positively to scratch tests with the 1:50 concentration. For these tests, glycero-saline solutions in 1:100, 1:250, and 1:500 concentrations of both non-precipitated

TABLE V. SCRATCH TEST TITRATIONS

	Alternaria MMP 3-A (Not Precipitated)						Alternaria MMP 3-B (Acetone-Precipitated)					Investigator (No. of Patients)
	++++	+++	++	+	± to −		++++	+++	++	+	± to −	
1:50 (65,000 PNU)	12					1:50 (65,000 PNU)	12					
1:100	5	3	4			1:100	4	5	3			Halpin
1:250		2	5	2	3	1:250		1	5	2	4	(12)
1:500			1	2	9	1:500			2		10	
1:50		2	1			1:50	2	1				Etter-
1:100		1	2			1:100		1	2			Raymer-
1:250			1	2		1:250			3			Jackson
1:500			3			1:500			2	1		(3)
1:50			1	1		1:50			1	1		
1:100			1	1		1:100				1	1	Prince
1:250				1	1	1:250				1	1	(2)
1:500				1	1	1:500					2	

In 17 patients: 1:50 100% diagnostic
1:100 100% diagnostic
1:250 13/17 (76%) diagnostic
1:500 7/17 (35%) diagnostic

In 17 patients: 1:50 100% diagnostic
1:100 16/17 (94%) diagnostic
1:250 12/17 (71%) diagnostic
1:500 5/17 (29%) diagnostic

(MMP-3-A) and acetone precipitated (MMP-3-B) Alternaria extracts were employed (Table V). Allowing for differences in patient sensitivity, and for individual variation in interpretation of test results according to the particular standards of each investigator, the 1:100 concentration was uniformly diagnostic in the seventeen patients with the regular MMP Alternaria extract, and was diagnostic in sixteen patients with the acetone-precipitated extract.

DISCUSSION

The allergenic material produced during the growth process, together with metabolites of sufficient molecular complexity that they are also non-dialyzable, constitutes the total content after dialysis of our modified synthetic culture broth. The assumption that molecular equilibrium is involved between the greater volume of liquid culture broth and the smaller mass of pellicle would explain the total higher allergen content of broth in which the pellicle has grown to maturity, and in which it has, in effect, been *extracted* by the broth during the entire growth process. At the same time, the doubtless production of complex metabolites during the growth process must also be remembered. In the present state of our knowledge, it is impossible to distinguish between substances extracted from the pellicle on the one hand, and growth metabolites in the broth on the other, as to which gives the broth its high allergen content. We believe it is entirely possible that metabolites in the broth, which would not be present in appreciable concentration in simple pellicle extracts, may themselves be allergenic. Thus, we must conclude that possibly *two* sources of skin reactive fractions may explain the superior allergen content of culture broth. Schaffer and his collaborators have also appreciated the high allergen content of culture broth.[8]

Early in our experiments with MMP extracts, we questioned the need for acetone precipitation, which had been an indispensable step in the preparation of Type 33 extracts. Acetone precipitation would produce a superior extract only if it accomplishes *selective* separation of allergenically active from less active or totally inactive fractions of the mold materials contained in the dialyzed MMP broth. It appears that acetone precipitation does not fractionate the active principles in these extracts, nor is its action quantitative or predictable. Furthermore, precipitation ordinarily is not complete, resulting in greatly reduced yields. Following these observations, and our failure to demonstrate clinical superiority of precipitated extracts, acetone precipitation was abandoned in routine MMP extract preparation.

In evaluating our results from skin testing with the MMP extracts, we wish to call attention to an important point. This concerns the classification of the patients selected for the tests, in respect to whether they are sensitive to the molds being studied. It is to be noted that Halpin, Talbott, Bartlett and Prince regarded sensitivities in their patients as differing somewhat be-

tween the dematiaceous molds, while the other investigators found sensitivity in their patients to extend throughout the entire dematiaceous series. These differences may reflect geographic variations, differing degrees of sensitivity in the admittedly small groups of patients studied, or diagnostic uncertainties resulting from prior testing with unpredictable extracts.

These considerations must be borne in mind in interpreting the performance of the MMP extracts. Particularly is this true with Hormodendrum (which had a diagnostic efficiency of only 40 per cent by scratch tests and 54 per cent by intradermal tests in the 1:100,000 dilution) in patients considered to be sensitive to Hormodendrum. We have observed similar lack of reactivity to Type 33 Hormodendrum extracts, and have made further confirmations in studies in progress with other MMP extracts of Hormodendrum. We believe that the allergenic importance of Hormodendrum has been over-emphasized in the past, because of its frequent isolation in air analysis studies, and because tests with Hormodendrum often, but not invariably, react in patients sensitive to other dematiaceous molds, particularly Alternaria. Hormodendrum appears to possess some dematiaceous family allergens, as revealed by its reactions on intradermal tests at the higher concentrations, but it rarely contains major generic allergens. Several of our patients classified as sensitive to Hormodendrum may have been generic-sensitive or dematiaceous family-sensitive.

The fact that some positive reactions were reported from scratch or intradermal tests in presumably non-sensitive patients raises further the question of proper diagnostic classification. We believe we have obtained true diagnostic tests in a few patients for the first time with these more potent allergens. In other instances, we might be dealing with low-grade dematiaceous family sensitization, because several of these patients were considered sensitive to one or more other dematiaceous molds. Also, some of these "non-sensitive" patients may have been classified improperly because of prior tests with extracts of poor diagnostic efficiency. The small number of "irritating" reactions from scratch tests in this group could, then, be truly positive tests reflecting mold sensitivities; the increase in the number of such reactions in the intradermal tests with stronger concentrations supports this possibility. To repeat, we feel that these "irritating" reactions pose a problem of reclassification, probably on the basis of dematiaceous family sensitization, in many of our "non-sensitive" patients.

CONCLUSION

We have reviewed data justifying the use of culture broth as a source of mold allergen, and have presented clinical studies with mold extracts prepared from broth. These extracts, produced from mold cultures grown in synthetic media and free of all extraneous substances, are specifically reactive, with predictable uniformity assured by weight-volume standardization. These highly reliable extracts may be diagnostic for patients not previously considered to be mold-sensitive.

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CLINICAL EVALUATIONS

Clinical evaluations are so beset by external forces which may affect them that every possible control measure must be applied if valid and durable results are to be obtained. Every effort must be made to insure the suitability of the method of exploration. The selection of the proper dosage range is vital and the selection of the proper subject is equally critical in the design for clinical evaluation. As far as possible, all external disturbances should be eliminated. Data must be collected promptly. Treatments must be randomized. In addition to the use of the placebo, the double blind control should also be used whenever and wherever it is feasible. It will prevent false positive interpretations, but it cannot prevent a false negative result. There is no conceivable disadvantage in the application of the double blind control, only protection against spurious data. However, it must be used to deal only with bias and psychic forces which cannot be otherwise eliminated, for truth will not validate otherwise poorly designed experiments.—Walter Model, Cornell University Medical College, New York. The Sensitivity and Validity of Drug Evaluations in Man. *Clinical Pharmacology and Therapeutics*, 1:769 (Nov.-Dec.) 1960.

TREATMENT OF HAY FEVER WITH EMULSIFIED POLLEN EXTRACTS

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THE PRESENT-DAY multiple injection treatment of hay fever has changed very little since it was first described by Noon[1] and by Freeman[2] in 1911. Various attempts have been made to improve the method of treatment but none has become generally accepted. In 1940, Freund and McDermott[3] demonstrated enhancement of antibody formation with Freund's adjuvant, an emulsion of extract and mycobacteria in mineral oil. Loveless[4] and Brown[5-10] have published papers on treatment of hay fever with emulsified extracts.

MATERIALS AND METHODS

The materials used were supplied by Brown, and the method employed was that which he described.[9] To 2.0 ml of sterile mixture of 1 part Arlacel A (the emulsifying agent) and 9 parts of Drakeol 6 VR (a refined mineral oil), 1.0 ml of pollen extract, 0.4 ml of epinephrine (1:100) or ethylnorepinephrine (1:50) (Bronkephrine®, Breon) and 0.6 ml of buffered saline were added. The mixture was then emulsified in a closed system consisting of two 10 cc Luer-lok syringes connected by a double-hub emulsator. The concentrations of the initial extracts were 40,000, 20,000, and 10,000 p.n.u. per ml. The final emulsions contained 10,000, 5,000, and 2,500 p.n.u. per ml.

Each patient was tested with one or more of the following concentrations of extract: for pressure puncture tests, 20,000 p.n.u./ml in 50 per cent glycerine; for intracutaneous tests, solutions containing 10, 100, 1000, or 2000 p.n.u. per ml; for conjunctival testing, non-glycerinated extracts containing 5, 10, 20, 40, 75, 150, 300, 600, 1200, 2500, 5000, 7500, 10,000, 15,000, or 20,000 p.n.u./ml were used.

Intracutaneous tests and pressure puncture tests were read as negative, slight, moderate, or marked, according to the size and regularity of the shape of the wheal. Negative indicated no appreciable change in the character of the wheal; slight, indicated a small increase in the size of the wheal; moderate, considerable increase in the size of the wheal, at least three times the diameter of the original wheal; marked, any wheal showing clear-cut pseudopodia. Marked reactions were also classified as marked + to marked ++++ depending on the size of the wheal.

Following Brown's recommendations, as used at the time, patients who

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showed a positive conjunctival test response received the dose shown in Table I.

Table II shows the dose given to patients according to the concentration of extract to which they respond with a marked reaction.

TABLE I. DOSAGE SCHEDULE

Positive Conjunctival Test	Dose Administered
20 p.n.u./ml	500 p.n.u.
40	1000
75	1500
150	2000
300	2500
600	5000
1200	6000
5000	7500
10,000	10,000

TABLE II. DOSAGE SCHEDULE

Skin-Test	Dose Administered
P.P.P.	2500 p.n.u.
10-100 p.n.u./ml	5000
1000	7500
2000	10,000

Patients who responded with a positive pressure reaction with pseudopodia received up to 2500 p.n.u. of emulsified extract.

Emulsified extracts were administered only where there was a correlation between the tests, the clinical symptoms, and the seasonal occurrence of these symptoms.

If there was a discrepancy between the degree of sensitivity indicated by the different types of tests, the test giving the indication of greatest sensitivity was used as the guide in determining the dose given.

Each patient received two tablets of Fedrazil® (Burroughs, Wellcome & Co.) one-half hour before the treatment was begun. This was followed by the subcutaneous injection of 0.1 ml of epinephrine 1:1000, one-half inch proximal to the proposed site of the injection. A spot on the arm, over the deltoid muscle, was marked with a small dot of Merthiolate®. The calculated amount of emulsified extract was transferred to a 1 ml tuberculin syringe. A disposable number 25 gauge needle, ⅝ inches long was affixed and the injection was given in four equal parts at fifteen to twenty-minute intervals, using the same spot for each part of the injection. After the needle was *in situ*, the plunger was drawn back to make sure that no blood was aspirated. The syringe was then rotated on its vertical axis as each part of the injection was administered. As the needle was withdrawn each time, the patient firmly sealed the site of the injection with his finger in order to occlude any local blood vessels which might have been traversed and also to prevent any leakage of the emulsion. Following the injections each patient took six 50 mg Perazil® tablets (Burroughs, Wellcome & Co.) during the ensuing forty-eight hour period and three 0.75 mg Deronil® tablets (Schering) during the ensuing twenty-four hours. All patients were asked to keep a daily record of symptoms during the pollen season on the chart illustrated by Figure 1.

Thirty-eight patients received, in all, eighty-two injections of emulsified extracts. Seventeen of these patients had suffered from late Spring hay

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NAME _____ MONTH _____ Year _____

DATE	SNEEZING				BLOCKED NOSE				NASAL DISCHARGE						ITCHY EYES				TEARING				COUGH				WHEEZING				SHORTNESS OF BREATH				OTHER COMPLAINTS (Specify)
	None	Occasional	Moderate	Severe	None	Occasional	Moderate	Severe	None	Occasional	Moderate	Severe	Watery	Green	Yellow	None	Occasional	Moderate	Severe	None	Occasional	Moderate	Severe	None	Occasional	Moderate	Severe	None	Occasional	Moderate	Severe	None	Occasional	Moderate	Severe	
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Have you had previous treatment? ___ Pills ___ Injections ___ Both ___ Results _____

How do your symptoms this month compare to the same month last year? _____

Other comments:

Fig. 1.

fever. These patients were treated with emulsified extract containing a mixture of June Grass, Sweet Vernal Grass, Red-top, Orchard Grass, Meadow Fescue and Timothy Pollen extracts. Each of the seventeen late Spring hay fever patients also had suffered from the Fall type of hay fever. These patients each received an injection of emulsified extract of short ragweed pollen. In addition to the seventeen patients who had previously received the injections of emulsified English plantain extract, nine of the other Fall type hay fever patients received an injection of emulsified English plantain extract.

TABLE III. DOSE OF EMULSIFIED MIXED GRASS POLLEN EXTRACT INJECTED

Dose (in p.n.u.)	1500	2500	5000	10,000
Number of patients	1	6	3	7

Table III shows the dosage of emulsified mixed grass pollen extract administered. The dose ranged from 1500 to 10,000 p.n.u.

RESULTS

The seventeen late Spring hay fever patients included four female patients, ranging in age from thirteen to thirty-five years and thirteen male patients, ranging in age from ten to fifty-seven years. Thirteen of the patients treated for late Spring hay fever reported good results; four, fair results; and none, poor results. The data concerning the late Spring hay fever patients are summarized in Table IV.

Table V shows the dosage of emulsified English plantain extract administered.

The dose of emulsified English plantain extract injected ranged from 2500 to 10,000 p.n.u.

The sixth table shows the dose of emulsified short ragweed extract administered.

Thirty-eight patients suffered from Fall type hay fever. This group included fifteen female patients, ranging in age from thirteen to fifty-nine years, and twenty-three male patients ranging in age from ten to sixty-six years. Of the thirty-eight Fall hay fever patients, twenty-five reported good results; six, fair results; and seven, poor results. The data concerning the Fall hay fever cases, are summarized in Table VII.

The results of treatment are listed in Table VIII.

REACTIONS

Fifteen patients suffered eighteen reactions. These consisted of urticaria, angioneurotic edema, bronchial asthma, generalized pruritus, and diffuse non-pitting edema of the arm. None of the reactions was so severe as to dis-

TABLE IV. LATE SPRING HAY FEVER

No.	Patient	Sex	Age	Grasses*					English Plantain*					Result
				Previous Top Dose of Aqueous Extract	Tests**			Emuls. Extract Given	Previous Top Dose of Aqueous Extract	Tests**			Emuls. Extract Given	
					I.C.	P.P.P.	Oph.			I.C.	P.P.P.	Oph.		
1	F.M.	F	31	2500	100	—	75	2500	2500	2000	—	—	10000	Fair
2	H.S.	M	51	5000	2000	—	—	10000	5000	2000	—	—	10000	Good
3	W.L.	M	34	4000	2000	—	—	10000	4000	2000	—	—	10000	Good
4	R.L.	M	54	2500	10	+	150	2500	3000	2000	—	—	10000	Good
5	D.S.	M	15	?†	20000	—	20000	10000	?**	2000	—	—	10000	Fair
6	A.S.	M	56	?†	100	—	150	2500	?**	—	+	300	2500	Fair
7	E.S.	M	41	?†	—	+	150	2500	?**	—	+	5000	3750	Good
8	N.P.	F	13	5000	2000	—	—	10000	5000	2000	—	—	10000	Good
9	H.F.	M	56	?†	—	+	75	2500	?**	1000	—	10000	7500	Good
10	G.M.	M	10	?†	—	+	150	2500	?**	100	—	10000	7500	Fair
11	K.L.	M	57	800 gel§	1000	—	20000	10000	1500	1000	—	—	7500	Good
12	W.V.	M	27	80‡	100	+	75	1500	200‡	500	+	1200	3750	Good
13	B.C.	F	35	1500 gel§	100	—	2500	5000	1500 gel§	2000	—	—	10000	Good
14	D.L.	F	18	?†	2000	—	10000	10000	?†	2000	—	—	10000	Good
15	A.C.	M	16	100‡	100	—	75	5000	100‡	1000	—	20000	7500	Good
16	M.L.	M	55	2000 gel§	2000	—	10000	10000	2000 gel§	2000	—	15000	10000	Good
17	C.B.	M	36	5000	2000	—	150	5000	5000	2000	—	—	10000	Good

*P.N.U. per cc.

**Strength of test giving strongest reaction.

†Treatment given elsewhere in previous years. Dosage unknown.

‡First season of treatment. Switched to emulsion therapy.

§Pollen extract in gelatin.

TABLE V. DOSE OF EMULSIFIED ENGLISH PLANTAIN EXTRACT INJECTED

Dose (in p.n.u.)	2500	3750	5000	7500	10,000
Number of patients	1	2	3	6	15

TABLE VI. DOSE OF EMULSIFIED SHORT RAGWEED EXTRACT INJECTED

Dose (in p.n.u.)	1500	1875	2500	3000	3750	5000	7500	10,000
Number of patients	1	4	8	1	2	6	4	12

TABLE VII. FALL TYPE HAY FEVER

No.	Patient	Sex	Age	Ragweed*					English Plantain*					Result
				Previous Top Dose of Aqueous Extract	Tests**			Emuls. Extract Given	Previous Top Dose of Aqueous Extract	Tests**			Emuls. Extract Given	
					I.C.	P.P.P.	Oph.			I.C.	P.P.P.	Oph.		
1	F.M.	F	31	2500	2000	–	20000	10000	2500	2000	–	—	10000	Good
2	H.S.	M	51	5000	2000	–	20000	10000	5000	2000	–	—	10000	Good
3	W.L.	M	34	5000	100	+	5000	2500	4000	2000	–	—	10000	Good
4	R.L.	M	54	3000	2000	–	—	10000	3000	2000	–	—	10000	Good
5	D.S.	M	15	?†	10	+	300	2500	?**	2000	–	—	10000	Poor
6	A.S.	M	56	?†	1000	–	2500	5000	?**	—	+	300	2500	Fair
7	E.S.	M	41	?†	—	+	600	2500	?**	—	+	5000	3750	Good
8	N.P.	F	13	5000	2000	–	—	10000	5000	2000	–	—	10000	Poor
9	H.F.	M	56	?†	10	+	600	1875	?**	1000	–	10000	7500	Good
10	G.M.	M	10	?†	1000	–	—	7500	?**	100	–	10000	7500	Good
11	K.L.	M	57	600	2000	–	—	10000	1500	1000	–	—	7500	Good
12	W.V.	M	27	200	10	–	5000	5000	200†	500	+	1200	3750	Poor
13	B.C.	F	35	1300 gel§	1000	–	20000	7500	1500 gel§	2000	–	—	10000	Good
14	D.L.	F	18	?†	1000	–	5000	7500	?**	2000	–	—	10000	Poor
15	A.C.	M	16	100‡	1000	–	20000	7500	100†	1000	–	20000	7500	Fair
16	M.L.	M	55	2000 gel§	1000	–	1200	5000	2000 gel§	2000	–	15000	10000	Good
17	C.B.	M	36	5000	2000	–	15000	10000	5000	2000	–	—	10000	Good
18	I.G.	F	16	—	10	+	1200	1875	—	—	–	—	—	Good
19	H.G.	F	26	?**	10	+	1200	2500	—	—	–	—	—	Fair
20	M.M.	F	53	?**	10	+	600	1875	—	—	–	—	—	Poor
21	R.L.	M	10	1250	1000	–	2500	5000	2000	2000	–	—	10000	Good
22	J.S.	M	52	?	10	–	300	3750	?	100	–	2500	5000	Good
23	T.T.	M	25	—	2000	–	—	10000	—	—	–	—	—	Good
24	R.P.	F	59	2400 gel§	100	–	2500	5000	—	—	–	—	—	Good
25	I.K.	F	26	5000	2000	–	—	10000	5000	2000	–	—	10000	Good
26	R.A.	F	36	50 gel§	10	+	2500	1875	—	—	–	—	—	Good
27	M.W.	F	60	?	10	+	150	2500	—	—	–	—	—	Good
28	K.B.	F	35	1400	—	+	2500	5000	5000	1000	–	—	7500	Poor
29	A.A.	F	40	?	100	–	5000	3750	—	—	–	—	—	Fair
30	A.D.	M	46	1800	100	+	600	2500	5000	100	–	5000	5000	Fair
31	S.D.	F	39	1000	10	–	1200	3000	—	10	–	2500	5000	Good
32	J.W.	M	40	—	10	+	1200	2500	—	1000	–	10000	7500	Poor
33	S.G.	M	66	—	10	+	20000	2500	—	—	–	—	—	Fair
34	I.K.	M	35	5000	2000	–	—	10000	—	2000	–	—	10000	Good
35	L.K.	M	12	5000	2000	–	—	10000	5000	2000	–	—	10000	Good
36	N.B.	M	53	?	10	+	150	1500	—	—	–	—	—	Good
37	J.U.	F	42	.05 of 1:50	1000	–	—	10000	—	—	–	—	—	Good
38	S.B.	M	29	—	1000	–	10000	10000	—	2000	–	—	10000	Good

*P.N.U. per cc.

**Strength of test giving strongest reaction.

†Treatment given elsewhere in previous years. Dosage unknown.

‡First season of treatment. Switched to emulsion therapy.

§Pollen extract in gelatine.

TABLE IX. REACTIONS

Date	Name	Age	Sex	Pollen Emulsion	Tests			Emuls.* Extract Given	Interval	Reaction	Duration	Result
					P.P.P.	I.C.	Oph.					
5 /2/59	H.F.†	56	M	Grass	Mkd.+++	—	75	2500	4 hrs.	Urticaria, angioneurotic edema, B.A.	12 hrs.	Good
4/29/59	A.C. †	16	M	Grass	Mod.	100 Mkd.++	150	5000	1 hr.	Urticaria	12 hrs.	Good
5/ 4/59	G.M.†	10	M	Grass	Mkd.+++	—	150	2500	6¼ hrs.	Urticaria, B.A.	6 hrs.	Fair
5/ 2/59	E.S.†	41	M	Grass	Mkd.+++	—	150	2500	6-7 hrs.	Diffuse non-pitting dependent edema of arm	48 hrs.	Good
5/ 2/59	A.S.†	56	M	Grass	Mkd.++	100 Mkd.++	150	2500	1 hr.	Flushing, pruritus	12 hrs.	Fair
5/22/59	W.V.	27	M	Eng. Pl.	Mkd.+	—	1200	3750	20 min.	Urticaria	2 hrs.	Good
5/26/59	G.M.	10	M	Eng. Pl.	—	100 Mkd.++	10 T	7500	30 min.	Sl. urticaria in controlateral arm	2 hrs.	Fair
5/27/59	A.S.	56	M	Eng. Pl.	Mkd.++	—	600	2500	3-4 hrs.	Slight itching of nose	2-3 hrs	Fair
6/17/59	H.F.	56	M	Rag.	Mkd.+	10 Mkd.+	600	1875	40 min.	General pruritus and erythema. Sl. B.A.	3-4 hrs.	Good
6/16/59	H.G.	26	F	Rag.	Mkd.++	10 Mkd.+++	1200	2500	24 hrs.	Diffuse non-pitting edema of arm	24 hrs.	Fair
6/19/59	S.B.	29	M	Rag.	—	1000 Mkd.	10 T	10000	1¾ hrs.	General pruritus and urticaria	24 hrs.	Good
6/23/59	D.S.	15	M	Rag.	Mkd.+	10 Mkd.+++	300	2500	3 hrs.	Tightness in chest. Urticaria, angioedema	8 hrs.	Poor
6/16/59	R.A.	36	F	Rag.	Mkd.+++	10 Mkd.+++	2500	1875	15 min.	Generalized pruritus	12 hrs.	Good
6/10/59	J.S.	52	M	Rag.	Mod.	10 Mkd.+	300	3750	2½ hrs.	Urticaria both arms. Delayed B.A.	12 hrs.	Good
6/24/59	D.L.	18	F	Rag.	—	1000 Mkd.	5T	7500	1½ hrs.	Urticaria	8 hrs.	Poor
6/17/59	R.L.	10	M	Rag.	—	1000 Mkd.++	2500	5000	2 hrs.	B.A.	8 hrs.	Good
7/ 7/59	M.M.	53	F	Rag.	Mkd.+++	10 Mkd.++++	600	1875	20 min.	Pruritus and urticaria	12 hrs.	Poor
6/24/59	S.D.	39	F	Rag.	—	10 Mkd.+++	1200	3000	10 min.	Itchy palms, sneezing	3 hrs.	Good

*P.N.U.

†Epinephrine or Bronkephrine® added after initial emulsification.

courage the patients from receiving additional injections of emulsified extracts. The first five reactions could have been prevented. The grass pollen extracts which were originally supplied to me had been previously emulsified. However, this group of emulsified extracts contained neither epinephrine nor Bronkephrine®. One of these was to be added to the previously emulsified extracts and the extract was then to be re-emulsified just prior to use.

TABLE VIII. RESULTS OF TREATMENT WITH INJECTIONS OF EMULSIFIED POLLEN EXTRACTS

	Late Spring Hay Fever	Fall Type Hay Fever
Good	13	25
Fair	4	6
Poor	0	7

We did not take into account the fact that, under the conditions of the study, any addition to the emulsion might cause some of the emulsion to break down. These patients, therefore, received an incompletely emulsified extract. When it was realized what had occurred, the extracts were not emulsified, thereafter, until all of the ingredients had been added.

All batches of emulsion were checked both by microscope and also by placing a drop of the emulsion into a beaker of water and observing the drop for maintenance of sphericity. Because we had been using number 18 and number 20 gauge emulsators at that time, the droplets of emulsified extract were not as fine as those now obtainable with finer gauge emulsators. Although all emulsions were apparently satisfactory, it is possible that there may have been a small amount of unemulsified extract present which we could not detect. The reactions occurred chiefly among those patients whose tests indicated the greatest degree of sensitivity and this would seem to indicate that there had been an excess of unemulsified extract present.

It is also possible that when the ophthalmic test was used as a guide, the reaction was read at a higher level (injection of the conjunctiva) than that recommended by Brown (injection of the caruncle). This may have resulted in some of the patients receiving a somewhat higher dose than that which Brown might have administered.

It was also observed that in some cases in which the ophthalmic test was performed, sneezing, and rhinorrhea preceded any changes in the eye. I have concluded that when this occurs, it should be considered a positive reaction. Another reason for the reactions may have been that repeated injections into the supposed same site may have lacerated small blood vessels and caused immediate general circulation of both unemulsified and emulsified extract. The data regarding reactions are summarized in Table IX.

SELECTED CASE HISTORIES

Abstracts with Comments

E.S., a man, aged forty-one, baker. Spring and Fall hay fever, twenty-five years. Discontinued previous treatment in 1950 because of severe local and systemic reactions, Tests—Mixed grasses: P.P.P., Mkd ++++; English plantain: P.P.P., Mkd ++; Short Ragweed: P.P.P., Mkd ++. Received the following doses of emulsified pollen extract: Mixed grasses, 2500 p.n.u.; English plantain, 3750 p.n.u.; and Short ragweed, 2500 p.n.u. This was one of the patients who received the emulsified grass pollen extract to which the epinephrine was added following the initial emulsification. Six to seven hours after the injection the patient began to have diffuse non-pitting edema of the arm which persisted for forty-eight hours. No reaction after subsequent injections of emulsified extract. Result: good.

Comment.—This case illustrates the occurrence of a severe local reaction following the use of an incompletely emulsified extract in an extremely sensitive patient.

H.F., a man, aged fifty-six, physician. Fall type hay fever, forty years; Late Spring hay fever, fifteen years. Discontinued previous treatment because of severe local and systemic reactions. Tests—Grasses: P.P.P., Mkd +++; English plantain: 1000 p.n.u., i.c., Mkd ++; Ragweed: P.P.P., Mkd +. Received the following doses of emulsified extracts: Mixed grasses, 2500 p.n.u., English plantain, 2500 p.n.u., and Short ragweed, 1875 p.n.u. This patient also received the emulsified mixed grass pollen extract to which the epinephrine had been added following initial emulsification. Four hours after receiving the emulsified grass extract, the patient experienced generalized urticaria and angioneurotic edema and bronchial asthma. He had no reaction following the injection of emulsified English plantain extract. Forty minutes following the injection of emulsified ragweed pollen extract he began to suffer from mild generalized pruritus with generalized erythema and a feeling of slight heaviness in the chest. Symptoms lasted two to four hours. The patient commented, "Much, much better. Last year I took eight to twelve antihistamine tablets per day. Wonderful result from one-day injections."

Comment.—This case illustrates the occurrence of a systemic reaction following the use of an incompletely emulsified extract in a highly sensitive patient.

Both the above cases, also illustrate the fact that when completely emulsified extracts are used, doses of extract, which might be expected to cause severe reactions if unemulsified extract had been used, may safely be administered.

B.C., female, secretary, aged thirty-five. Late Spring and Fall hay fever for eleven years. Did well with previous treatment but her dose could never exceed 1500 p.n.u of pollen extract in gelatin because of severe local and systemic reactions. Intracutaneous skin tests—Grasses: 100 p.n.u., Mkd; English plantain: 1000 p.n.u., Mkd; Short Ragweed: 1000 p.n.u., Mkd. Received the following doses of emulsified pollen extracts: English plantain, 10,000 p.n.u.; Grasses, 5000 p.n.u.; and Ragweed 7500 p.n.u. No reactions of any type experienced. Result: good.

Comment.—This case illustrates the fact that large doses of emulsified extract may be administered safely, without causing reactions, to a patient who could previously tolerate only small doses of unemulsified extract.

M.M., housewife, aged fifty-three. Fall hay fever, twelve years. No relief from previous multiple injection treatment. Tests—Ragweed: P.P.P., Mkd +++; I.C., 10 p.n.u., Mkd ++++; Ophthalmic, 600 p.n.u.; Dust: Mkd; English plantain: 500 p.n.u., moderate; Feathers: Mkd. Received 1875 p.n.u. emulsified ragweed pollen extract divided in three equal doses. Twenty minutes following the third dose patient suffered from generalized pruritus and urticaria which lasted for twelve hours. The patient reported a poor result. This may have been due to the fact that her secondary allergens, house dust, English plantain, and feathers were not included in her program of treatment because of the fact that they were not available to me at the time.

D.L., a young female student, aged eighteen. Hay fever symptoms from April to October for ten years. She was treated by hyposensitization elsewhere for several years with good results. The patient refused to undergo complete allergy studies but was willing to chance pollen tests and treatment with pollen extracts alone. Intracutaneous tests—Grasses: 2000 p.n.u., moderate; English plantain: 2000 p.n.u., moderate; Ragweed: 1000 p.n.u., marked. Received the following doses of emulsified pollen extracts: Grasses, 10,000 p.n.u.; English plantain, 10,000 p.n.u.; and Ragweed, 7500 p.n.u. One and a half hours after the emulsified ragweed extract was administered, she broke out in urticarial wheals which persisted for eight hours. She reported good results for her late Spring hay fever and poor results for her Fall hay fever. The patient spent the summer working at a race track. I feel that the patient's refusal to permit a complete allergy study was probably responsible for the failure of the treatment, since I feel that she probably had secondary allergens of importance which were responsible for her symptoms during the Fall hay fever season.

Comment.—The previous two cases illustrate the necessity of performing comprehensive allergy studies on every patient and either eliminating (as in the case of food and animal dander) or treating (as in the case of dust or molds) secondary allergens of importance, whichever may be feasible or indicated.

R.A., woman, aged thirty-six, housewife. Fall hay fever for twenty years. Dose of unemulsified extract could not exceed 50 p.n.u of ragweed extract in gelatin without provoking severe local and systemic reactions. Tests: Ragweed, P.P.P., Mkd +++; Intracutaneous, 10 p.n.u., Mkd +++; Conjunctival, 2500 p.n.u. She was given 1875 p.n.u. emulsified ragweed extract divided into three equal doses. Fifteen minutes after the last dose she developed generalized pruritus which lasted twelve hours. Results: good.

S.B., man, aged thirty, auto body repairman. Fall hay fever for four years. I first saw him in 1958 at the height of the Fall hay fever season, so severely distressed that he needed adrenal steroids to provide relief of symptoms. This was one of the most severely affected patients that I have ever seen. The patient discontinued multiple injection treatment because of the occurrence of severe local reactions. Tests: Intracutaneous, English plantain, 2000 p.n.u., moderate; Ragweed, 1000 p.n.u., Mkd. Patient was given 10,000 p.n.u. of emulsified English plantain extract and 10,000 p.n.u. of emulsified ragweed extract, on different days, each divided into four equal doses. One and a quarter hours following the last dose of emulsified ragweed extract he developed generalized pruritus and urticaria which lasted twenty-four hours. Results: good.

Comment.—The previous two cases illustrate the fact that large doses of emulsified extract may be administered safely to highly sensitive patients.

The reactions in these cases did not occur until after the last fraction of the patient's injection had been given. The reaction may have occurred because of one of the reasons stated previously.

DISCUSSION

Thirty-eight patients received eighty-two injections of emulsified pollen extracts for treatment of late Spring or Fall hay fever, or both. If these patients had been treated with the multiple injection technique, each patient would have required at least fifteen injections, either preseasonally or perennially, in order to have received the amount of extract regarded by most allergists as necessary for hyposensitization. In other words, this group of patients would have needed at least 570 visits to have received the required amount of treatment, if the usual multiple injection technique had been used. Actually, this group of patients needed only eighty-two visits to accomplish the same purpose, which represented a saving of at least 488 visits. The majority of these patients did as well, if not better, than they had done with the multiple injection technique. The rate of reactions encountered was apparently high. The first five reactions occurred in those patients who received the emulsions to which epinephrine had been added after emulsification. The rate here is apparently 100 per cent. However, since these patients did not actually receive true emulsions of the extracts, these reactions, cannot really be counted. After excluding the first five reactions, we are left with an apparent rate of thirteen reactions in seventy-seven injections or almost 17 per cent. However, since each injection of emulsified extract represented fifteen or more injections of unemulsified extract, the corrected reaction rate is actually about 1 per cent. None of the reactions encountered was sufficiently severe to discourage the patients from continuing with additional injections of emulsified extracts and, in fact, thirty-five of these patients have already signified their intention of continuing with this same type of treatment for the forthcoming hay fever seasons.

The results were not apparently affected by the local or systemic reactions. Five of the reactions should have been foreseen and could have been prevented by not having made any additions to the emulsions after the initial emulsification. The other thirteen reactions occurred chiefly in highly sensitive patients, several of whom could not previously tolerate any injections of pollen extract whatsoever. They had had to be treated with oral medications, including corticosteroid hormones. Most of these patients did well following treatment with emulsified pollen extracts.

All patients should, as always, have comprehensive allergy studies performed, as has been customary in the past. Secondary allergens, such as dust, foods, molds, animal danders et cetera, which are proven to be of clinical importance in the patient's condition, should either be eliminated, where possible, or the patient should receive hyposensitization for those secondary allergens which cannot be eliminated but, for which suitable extracts are available.

Several factors must be taken into account in evaluating the results of treatment. Some of the patients may be "placebo reactors," while some may have a lower threshold of discomfort than others. The following factors may also affect the results of treatment: the variation of the pollen count from year to year, variation in the temperature, humidity, mold content of the air, emotional factors, incidental exposures to dust, paint, occupational, and other environmental allergens.

CONCLUSION

The treatment of hay fever by the use of emulsified pollen extracts is described and discussed. Abstracts of case histories of several patients are presented. It is concluded that with the continued improvements being made in the emulsions and in the techniques of administration, treatment with such emulsified extracts will prove to be one of the most significant advances made in the management of hay fever.

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DIRECTIONS FOR THE SCIENTIFIC CAREER

Observe facts, conceive a hypothesis, determine its value through one or several series of judiciously instituted experiments, give the interpretation or more accurately one interpretation of the facts and ascertain the excellence of this interpretation through strict criticism; generalize the results experimentally without forgetting that an investigation must be pushed to the end—these are the directions that I propose to young people on entering the scientific career.—MAURICE ARTHUS, *Philosophy of Scientific Investigation,* Baltimore, The Johns Hopkins Press, 1943.

COMPARISON OF HIGHER DOSAGE LEVELS USED IN THE CO-SEASONAL TREATMENT OF POLLINOSIS

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MOST allergists are generally agreed that maximum tolerated doses of pollen extracts should be reached prior to the onset of the pollen season. During the pollen season, however, smaller doses should be repeated at more frequent intervals. There seems to be a wide divergence of opinion, however, as to what constitutes adequate therapy, in terms of top dosage levels of pollen extracts, that should be reached during co-seasonal treatment.

Different approaches to the problems of co-seasonal treatment of pollinosis have been tried by various investigators. A brief review of these approaches is given. Wittich[1] advocated starting with 10-20 pollen units subcutaneously, an amount which should be increased by 20 units daily until adequate relief of symptoms is obtained. The intervals between injections should then be increased to two days, three days, and so on, for the duration of the season. Vaughan,[2] after years of clinical experiences, found that, in the majority of patients, a top dose of 80 pollen units, and not to exceed 200 units gave adequate relief when repeated at frequent intervals during the season. Rowe's[3] approach to this problem has been along similar lines, for he preferred to use small doses at frequent intervals. The range of these doses varies from 0.10 cc. of a 1:500,000 dilution of pollen extract up to 0.10 cc. of a 1:500 dilution (200 pollen units), according to the degree of the patient's sensitivity.

Other authors, such as Hansel,[4] prefer an even smaller dosage range, and give intracutaneous instead of subcutaneous injections. With this method, treatment is usually begun with 0.02 cc of that dilution which will produce a wheal about 15 to 18 mm in diameter as determined by skin testing. Subsequent doses are given every two to five days, and increased by 0.01 cc until satisfactory relief is obtained. With this intracutaneous method, 5 to 100 pollen units are considered optimum dosages. Sheldon[5] uses a similar method, and increases the dose of the intradermal injections until the patient experiences temporary relief of symptoms. He then repeats this same dosage every one to three days.

Waldbott,[6] on the other hand, describes a group of cases of seasonal pollinosis in which symptoms were not adequately controlled until dosages as high as 30,000 pollen units were used during the season. He states that in many cases, co-seasonal treatment is ineffective because the doses employed are too small, and that it is as important to increase the doses in a given

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TABLE I. CORRELATION OF DOSAGE LEVELS REACHED DURING CO-SEASONAL TREATMENT WITH DEGREE OF PATIENT'S SENSITIVITY

Case	Type of Allergy	Degree of Sensitivity	Antigens	Dosage Levels
1.	Asthma and hay fever	Slight	Mixed grasses and Bermuda	3,000 pollen units 3,000 pollen units
2.	Asthma and hay fever	Slight	Ragweed	3,500 pollen units
3.	Asthma and hay fever	Marked	Mixed grasses	5,000 pollen units
4.	Hay fever	Very marked	Mixed grasses and Bermuda	75 pollen units 75 pollen units
5.	Asthma and hay fever	Moderate	Ragweed	5,000 pollen units
6.	Asthma and hay fever	Slight	Mixed trees and grasses	5,000 pollen units 5,000 pollen units
7.	Hay fever	Marked	Mixed grasses and Bermuda	300 pollen units 300 pollen units
8.	Asthma and hay fever	Slight	Mixed grasses and Bermuda	3,000 pollen units 3,000 pollen units
9.	Hay fever and allergic rhinitis	Slight	Mixed grasses	3,500 pollen units
10.	Asthma, hay fever, and allergic rhinitis	Slight	Mixed grasses and Bermuda	1,500 pollen units 1,500 pollen units
11.	Hay fever and allergic rhinitis	Slight	Ragweed	4,000 pollen units
12.	Hay fever, insect allergy	Moderate	Mixed grasses and Bermuda	5,000 pollen units 5,000 pollen units
13.	Asthma and hay fever	Marked	Mixed grasses and trees	2,000 pollen units 2,000 pollen units
14.	Hay fever	Slight	Ragweed	1,000 pollen units
15.	Asthma and hay fever	Marked	Mixed grasses	90 pollen units
16.	Asthma and hay fever	Moderate	Mixed trees	240 pollen units
17.	Hay fever and allergic rhinitis	Moderate	Mixed grasses and Bermuda	2,500 pollen units 2,500 pollen units
18.	Asthma and hay fever	Slight	Mixed grasses	5,000 pollen units
19.	Hay fever	Slight	Ragweed	4,000 pollen units
20.	Asthma	Marked	Mixed grasses	2,000 pollen units
21.	Hay fever	Slight	Mixed grasses and Bermuda	5,000 pollen units 3,000 pollen units
22.	Asthma	Marked	Mixed grasses	1,500 pollen units
23.	Asthma, hay fever, and atopic eczema	N.D.	Mixed grasses and Bermuda	2,000 pollen units 2,000 pollen units
24.	Asthma and hay fever	Moderate	Mixed grasses and trees	26 pollen units 45 pollen units
25.	Asthma, hay fever, and nasal polyps	Slight	Mixed grasses and Bermuda	3,000 pollen units 3,000 pollen units
26.	Asthma and hay fever	N.D.	Mixed grasses	800 pollen units
27.	Asthma and hay fever	Slight	Mixed grasses	3,000 pollen units
28.	Asthma and hay fever	Moderate	Ragweed	4,000 pollen units
29.	Asthma and hay fever	Marked	Mixed grasses	4,000 pollen units
30.	Asthma and hay fever	Slight	Ragweed	1,500 pollen units
31.	Asthma and hay fever	Marked	Ragweed	3,000 pollen units
32.	Hay fever and allergic rhinitis	Slight	Mixed grasses	1,200 pollen units
33.	Asthma and hay fever	Very marked	Mixed grasses	5 pollen units
34.	Hay fever and allergic rhinitis	Slight	Mixed grasses	5,000 pollen units
35.	Asthma and hay fever	Very marked	Mixed trees	3,500 pollen units
36.	Hay fever and allergic rhinitis	Slight	Ragweed	2,000 pollen units
37.	Hay fever	Slight	Mixed grasses	2,000 pollen units
38.	Asthma, hay fever, and Nasal polyps	Slight	Mixed trees	4,500 pollen units
39.	Asthma and hay fever	Moderate	Mixed trees	2,000 pollen units
40.	Asthma, asthmatic bronchitis, and pulmonary emphysema	N.D.	Mixed grasses	2,500 pollen units
41.	Asthma and hay fever	N.D.	Mixed grasses	2,500 pollen units
42.	Asthma and hay fever	Slight	Ragweed	2,500 pollen units
43.	Asthma and hay fever	Moderate	Ragweed	3,000 pollen units
44.	Asthma and hay fever	N.D.	Mixed grasses and Bermuda	1,000 pollen units 1,000 pollen units
45.	Hay fever	Marked	Ragweed	100 pollen units
46.	Hay fever	Moderate	Mixed grasses and Bermuda	60 pollen units 950 pollen units
47.	Asthma and hay fever	Slight	Ragweed	3,500 pollen units
48.	Hay fever	Marked	Ragweed	600 pollen units
49.	Hay fever and allergic rhinitis	Slight	Mixed grasses	5,000 pollen units
50.	Hay fever	Moderate	Ragweed	260 pollen units
51.	Hay fever and atopic dermatitis	N.D.	Mixed grasses	2,000 pollen units
52.	Hay fever, allergic rhinitis and migraine	Slight	Mixed grasses and Bermuda	2,000 pollen units 2,000 pollen units
53.	Hay fever	Marked	Mixed grasses and Bermuda	1,500 pollen units 2,500 pollen units
54.	Hay fever and allergic rhinitis	Slight	Ragweed	2,500 pollen units
55.	Hay fever and allergic rhinitis	Marked	Ragweed	600 pollen units
56.	Hay fever and allergic rhinitis	Slight	Mixed trees	1,600 pollen units
57.	Asthma and hay fever	Marked	Ragweed	400 pollen units
58.	Hay fever	Moderate	Ragweed	2,500 pollen units
59.	Hay fever and allergic bronchitis	Slight	Mixed grasses	5,000 pollen units
60.	Hay fever and allergic bronchitis	Slight	Mixed grasses and Bermuda	5,000 pollen units 5,000 pollen units

N.D. Sensitivity tests not done because of age of patient.

case, as it is to keep them low in another. The method of Loveless[7] and other authors advocating higher dosage levels, is to give a short booster course for a total of 10,000 protein nitrogen units. This course appears to give adequate protection for most cases of ragweed-sensitive patients. Such treatment, however, was given pre-seasonally and not co-seasonally. Loveless' cases were carefully controlled by previous immunologic assays, and all had been under scrutiny for one to five years.

In general, it can be said that successful results in any given case depend upon the skill and judgment of the allergist.

The object of this investigation was two-fold: (1) to see if higher levels could be obtained without unnecessary local or systemic reactions, and (2) whether such higher dosage levels could be correlated with the relief of the patient's symptoms.

MATERIALS AND METHODS

Sixty cases of seasonal pollinosis were selected to fulfill the diagnostic requirements as follows:

1. A history of seasonal hay fever or asthma, or both, confined to one or more pollen seasons.
2. Adequate skin testing with scratch and intradermal tests using glycerinated pollen extracts for diagnosis. Conjunctival tests were done in a few cases where skin tests were negative.
3. Serial dilution tests were done in all cases, when practical.
4. A general physical examination was done with special emphasis on observing the nasal mucous membranes.
5. Nasal smears using Wright's stain for eosinophiles were routine.

Serial Dilution tests were performed with 1, 10, 100, and 1,000 Pollen or Noon units per mc, and were graded as very marked, marked, moderate, or slight according to the severity of skin reactions. An occasional case which was negative to the 1,000 unit strength was tested with the 10,000 unit strength. Although, in general, there was good correlation between the patient's sensitivity as determined by serial skin tests, and the amount of pollen extract he was able to tolerate, this was not so in all cases. Many patients who showed a marked skin reaction to the 1 unit strength were able to take fairly large doses of pollens without any difficulty during the season. On the other hand, the patients least sensitive, as indicated by skin testing, did not always tolerate the largest amounts of pollen extract (Table I).

No case was included in this series which did not have a minimum of one full season of co-seasonal therapy, and cases were limited to those patients who had not received specific treatment prior to the onset of their present season. A few patients who presented themselves for treatment shortly after their season had started were included. It was felt that these would be balanced by some cases which were started a week or two ahead of time.

The majority of these primary co-seasonal patients were followed up with perennial treatment of from two to ten years.

In this series of sixty patients, eight children and fifty-two adults were given co-seasonal treatment. There were twenty-seven cases of seasonal hay fever, three of seasonal asthma, and thirty of combined hay fever and asthma. Five patients were treated with tree pollen, eighteen patients with grass pollen, nineteen patients with ragweed pollen, fifteen patients were treated with both grass and Bermuda grass pollen, and three patients with both tree and grass pollen.

The conventional method of a series of graduated injections was employed by using aqueous pollen extracts. These extracts were (1) grass mixture containing June, Johnson, red top, sweet vernal and orchard grass in equal parts; (2) tree mixture containing oak, maple, sycamore, hickory and elm in equal parts; (3) ragweed mixture containing equal parts of giant and short ragweed; (4) Bermuda grass was given as a separate extract because of the long Bermuda grass season in this area. Other inhalant extracts were employed along with pollen extracts in those cases complicated by inhalant sensitivity to house dust, tobacco and dust, molds, feathers and animal hairs. Stock and autogenous respiratory vaccines were added for those cases of pollinosis complicated by infections.

TOP DOSAGE LEVELS

An arbitrary number of 5,000 pollen or noon units was used as a top dosage level. When a patient reached this top level and even though his symptoms were not well controlled, no further increases were made during the season. Any severe reaction during the course of treatment, either local or systemic was an indication to reduce dosage and to make no further increments during that season.

As might be expected, however, not all patients were able to reach a top dosage level of 5,000 pollen units. As shown in Table II, six cases fell within dosage levels of from 0-100 units, nine cases within 100-1,000 units, twelve cases within 1,000-2,000 units, twelve cases within 2,000-3,000 units, nine cases within 3,000-4,000 units and twelve cases within 4,000-5,000 units.

METHOD OF DOSAGE INCREMENTS

No definite schedule of increasing pollen extracts was used. If a patient had no local reaction to 20 pollen units, then increases of 30, 40, 50, 100, 150, and larger amounts were made, and continued until either the patient's clinical symptoms were effectively controlled, or a local reaction was obtained. It was found that many patients could tolerate increments of 500 to 1,000 pollen units during their season without any undesirable effects. The best guide to dosage increments was the development of any local reaction at the site of injection. This reaction was a clear warning to cease further increases. When this warning was not heeded, then a systemic reaction was the usual consequence if increases of extracts were continued. One patient,

who neglected to tell us of itching at the site of a prior injection, suffered a most severe systemic reaction following an increase of 10 pollen units. Fortunately, however such reactions were rare because normal inspection of the patient's arm was done after each injection.

ILLUSTRATION OF CASES WITH DETAILS OF PROCEDURE

Case 1.—W.S.P., a man, aged sixty-six years, first seen on June 24, 1958, with a history of seasonal asthma and hay fever starting about the first week in April. Symptoms had become so severe that he required the use of Isuprel Mistometer every two hours for relief, along with Amesec Capsules every four hours. The patient was a known cardiac and had one severe attack of coronary thrombosis in 1954. He was started on co-seasonal therapy with 10 pollen units of a Stock Grass Mixture containing (June, Johnson, red top, sweet vernal and orchard grass in equal parts), and 10 pollen units of Bermuda grass. This dosage was increased to 20 pollen units of each, then 40, 60, 80, 100, and 150 pollen units three times weekly. Then, larger dosage increments of 100, 200, 300 and 500 pollen units were made two times weekly and finally once a week until the end of the grass season in this area. At that time, a top dosage level of 3,000 pollen units each of grass mixture and Bermuda grass had been reached.

The patient was told to avoid the Isuprel Mistometer and, instead, was given a bronchodilator mixture containing potassium iodide, ephedrine and elixir terpene hydrate five times daily and Amesec Capsules to be taken only when necessary. After three weeks, the patient's symptoms were effectively controlled, and he had no further trouble for the rest of the grass season. There were no local or systemic reactions.

Case 2.—B.I., a woman, aged forty-one years, had a history of seasonal asthma and hay fever occurring every fall for thirty-four years. The patient was seen on September 3, 1945, with severe symptoms of pollinosis. Co-seasonal treatment was started with 10 pollen units of ragweed extract (50 per cent giant and 50 per cent short ragweed), which was increased to 20, 40, 70, 100 and 200 pollen units at daily intervals, then every two to three days. At the level of 200 units, a moderate local reaction in the form of itching and swelling at the site of injection was obtained. The dose of 200 units was repeated once, and again increased as follows: 300 pollen units, 500, 750, 1,000, 1,500, 2,000, 2,500, 3,000, and 3,500 pollen units two times weekly and then once a week until end of ragweed season. A second moderate local reaction occurred at the level of 1,500 units, but none after that. This is an example of a patient whose severe symptoms of pollinosis were effectively controlled after two weeks with rapid increases of ragweed extract to a fairly high dosage level (3,500 pollen units) given co-seasonally. There were only two moderate local and no systemic reactions.

Case 3.—R.R., a man, aged twenty-nine years, had a history of seasonal hay fever in the summer, and asthma in the fall for the past six years. Patient was seen on May 1, 1953, when co-seasonal treatment with grasses and pre-seasonal treatment with ragweed was started. He was given 5 pollen units of Stock Grass Mixture, and 5 pollen units of Ragweed Mixture. Dosages were rapidly increased at intervals of two to three days to 10, 20, 40, and 70 units of each extract, at which level there was a moderate local reaction to grasses. The 70 units of grass extract was repeated twice, and since there was no further reaction, dosage was again rapidly increased as follows: 100 pollen units, 200, 400, 700, 1,000, 2,000, 2,500, 3,000, 4,000 and 5,000 pollen units two times weekly and then once a week until the end of the grass

season. Pre-seasonal treatment with ragweed was carried to a maximum tolerated dosage of 10,000 pollen units prior to the start of the ragweed season.

ANALYSIS OF SERIES

The results of this investigation are summarized in Tables II and III. Table II shows the dosage levels reached with co-seasonal treatment in sixty cases of seasonal pollinosis, the reactions and the results obtained.

TABLE II. SHOWING DOSAGE LEVELS REACHED WITH CO-SEASONAL TREATMENT IN 60 CASES OF SEASONAL POLLINOSIS

Dosage Level	Number Cases	Reactions	Results
Below 100 pollen units	6	Systemic—1—Severe 2—Mild Local —Marked— 3 —Moderate—1 Mild— 1	Excellent— 1 Good — 4 Fair — 1
100-1,000 pollen units	9	Systemic—3—Mild Local —Marked— 3 Moderate—3	Excellent— 4 Good — 2 Fair — 3
1,000-2,000 pollen units	12	Systemic—None Local —Moderate—2	Excellent—10 Good — 2
2,000-3,000 pollen units	12	Systemic—1—Mild Local —Moderate—5 Mild— 1	Excellent—10 Good — 1 Fair — 1
3,000-4,000 pollen units	9	Systemic—None Local —Moderate—1 Mild— 1	Excellent— 8 Poor — 1
4,000-5,000 pollen units	12	Systemic—1—Mild Local— Marked— 1 Moderate—1 Mild— 1	Excellent— 9 Good — 1 Poor — 2
Above 5,000	0		
Total	60	Total— Systemic — 8 Local —24	Total—E —42 G —10 F — 5 P — 3

Highest Dosage Levels Reached During Co-Seasonal Treatment.—It was found that six patients were unable to tolerate amounts of pollen extracts greater than 100 pollen units, but that the remaining group or 54 patients were able to tolerate amounts varying from 100 to 5,000 pollen units. If one used 1,000 pollen units as an arbitrary dividing line, then forty-five patients or 75 per cent of the total number were able to tolerate amounts of pollen extracts greater than 1,000 units and fifteen patients were not.

Reactions.—In this series, there was one severe systemic reaction and seven mild systemic reactions manifested by hay fever or wheezing following injections, and twenty-four local reactions varying from mild, to moderate and marked. The remaining twenty-eight patients were free of local or systemic reactions. (See Table II). The three most severe systemic reac-

tions occurred at levels below 100 pollen units. The other five which were much less severe occurred at levels varying from 200 to 4,000 pollen units. This would indicate that if one can tolerate beyond the 100 unit level, the chances of a severe systemic reaction are much less than below this level.

Results of Treatment.—The correlation of treatment results with dosage levels was empirical. Patients were graded as excellent, good, fair and poor according to their own subjective responses. Excellent meant freedom of symptoms of pollinosis without antihistamines; good indicated marked relief of symptoms but with a necessity for antihistaminic agents; fair indicated a lesser amount of relief with antihistamines necessary for good control, and poor signified persistence of symptoms despite adequate dosage levels and symptomatic therapy.

According to this classification, forty-two were graded as excellent; ten, good; five, fair and three, poor (Table II). In regard to correlation of dosage levels with clinical improvement, there did not appear at first glance to be any definite relationship, because four cases which were graded as excellent fell into the dosage level groups below 1,000 pollen units, and one below 100 pollen units. In the two groups graded as having good and fair results, there were ten patients in whom levels of 1,000 pollen units were not reached and five patients who tolerated levels above 1,000 units. The three cases considered poor were those complicated by infections, in which control of patient's allergy was difficult because of underlying infections.

TABLE III. SHOWING FURTHER BREAKDOWN OF RESULTS OBTAINED IN 60 CASES OF SEASONAL POLLENOSIS

Dosage Level	Excellent	Good	Fair	Poor
Above 1,000 pollen units	37	4	1	3
Below 1,000 pollen units	5	6	4	0
Total cases	42	10	5	3
Per cent tolerating levels above 1,000 pollen units	88%	40%	20%	

A further breakdown of these figures according to results obtained in each treatment group shows a definite correlation of dosage levels with clinical improvement (Table III). In the excellent group, thirty-seven cases or 88 per cent of total cases in that group tolerated levels above 1,000 pollen units, whereas in the group graded good, only four cases of 40 per cent tolerated levels above this amount, and in the group graded fair, only one case or 20 per cent. This would indicate that in this small series of sixty cases, the best results were obtained in those patients who were able to tolerate levels above 1,000 pollen units as compared to those unable to tolerate levels above 1,000 units.

SUMMARY AND CONCLUSIONS

Sixty patients afflicted with seasonal pollinosis were given primary co-seasonal therapy.

An attempt was made to reach the highest dosage levels that the patient could tolerate.

It was found that forty-five of the sixty patients (75 per cent) were able to tolerate dosage levels greater than 1,000 pollen units with little or no undesirable reactions.

In this group were thirty-seven cases which were graded as excellent, four good, one fair, and three poor results.

It would appear that in our experience, higher dosage levels of aqueous pollen extracts during co-seasonal therapy were accompanied by better treatment results.

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MEDICAL COMMUNICATION

The medical profession is perhaps unique in its unselfish desire to share its discoveries and medical experiences with its colleagues, an altruistic gesture of benefit to all mankind. Most other discoverers profit monetarily from their discoveries but the physician who finds a prophylactic against some crippling condition or a cure for a fatal disease makes this information available without charge to every practitioner in the world so that each may employ it in his own practice and thus benefit humanity. In the words of Hewitt, "Most of the people who are in the fight against that enemy (disease) have something buoyantly admirable about them. Eagerly they give their secrets to each other, for the good of somebody else, who is unknown to either of them, and who cannot requite them for the benefits they have conferred."—SELMA DEBAKEY, Mediums of Medical Communication, *Journal of the Albert Einstein Medical Center,* 8:238 (Oct.) 1960.

RÉSUMÉ OF INSECT ALLERGY

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THE PURPOSE of this paper is to bring up to date the excellent résumés on Insect Allergy by Ethan Allan Brown in 1944 and Ely Perlman in 1955. Some of their material will be repeated since many of our references of necessity are the same. Some, I hope, will be new and interesting and that which is old can also be of interest.

The subject of insect allergy is a fascinating and ever widening topic. One of the earliest records is that of King Menes of Egypt, stung to death by a wasp or hornet in 2641 B.C. Medical literature begins somewhat more recently. In 1833, Brandt and Ratzenburg did a study on bee venom and likened it to viper poison. In 1877, Langer did the first thorough chemical examination of venom, invalidating formic acid as the cause of reactions. Early interest was chiefly centered about venom reactions of the stinging and biting insects with little realization that asthma and hayfever could be due to any part of the insect, body, hair, scales as well as the venom itself.

Many papers have been written describing fatal or near fatal reactions due to the stinging insects. This literature served to stimulate investigation of the chemical and allergenic properties of the insects, the venom, the immunologic mechanisms involved, the entomologic data including physiographic material and whatever other sources could be tapped to furnish a link between the clinical data and the antigenicity of the insects.

In the early 1900's, as the knowledge of immunology grew and developed, so did the work on insect allergy. In 1930, Benson and Seminov wrote a classic paper, "Allergy in its Relations to the Bee Sting." Tremendous activity has continued ever since with great emphasis in the last decade on immunologic studies. Braun, in 1925, published a report on allergic reactions in humans from sensitization to bee stings. He described the increasing severity of reactions following repeated stings and subsequent anaphylactoid reaction relieved by adrenalin. He also attempted desensitization with bee extract, following which the patient developed only mild symptoms after a bee sting. Many papers followed this, describing different methods of skin testing and treatment.

When discussing insect allergy, most of the Arthropods are included. The class Arachnida includes the spiders, mites and ticks. The class Hexopoda or Insecta contains the various orders that have been most extensively studied. The locusts, grasshoppers, roaches and crickets are of the Order Orthoptera; the Mayflies, of the Ephemeroptera; the caddis flies, of the

Trichoptera; the mosquitoes and houseflies, of the Diptera; and the most familiar—the honey bee, the bumble bee, the hornets, wasps, yellow jackets and ants—belong to the Hymenoptera.

The kinds and number of insects, even those commonly known, total a figure which staggers the imagination. The Hexopoda alone has more than a million varieties. The moths, butterflies, bees, wasps, hornets, yellow jackets, flies and mosquitoes comprise about 40 per cent; the beetles another 40 per cent; and the remainder about 20 per cent. One needs only to see entire walls of large buildings covered by swarms of Caddis and Mayflies, or mosquitoes so thick one cannot see past them, or grasshoppers covering hundreds of acres so completely that the ground is obscured, or swarms of butterflies sufficiently large to blot out a section of the sky, or even the common green Aphids covering a rose bush in the summer, to begin to comprehend the tremendous numbers of insects.

Some insects produce only one insect per egg, but such insects may produce thousands of eggs daily. The queen bee produces 2,000 eggs per day; some termites, over 40,000 daily. Some insects produce multiple progeny from one egg. The parasitic wasps may have as many as several thousand from a dozen eggs.

The actual dispersal of insects in, on, and above the earth is fantastic. Insects have been found in every climate from the tropics to the frozen north. They have been found below the earth's surface and up to 15,000 feet above the earth. The densest population is at about 1,000 feet; this is reduced 50 per cent at 2,000 feet; and reduced 50 per cent further at 3,000 feet. The stronger flying insects are located closer to the ground; the smaller, weaker ones are at higher altitudes; the wingless insects were collected at altitudes greater than 10,000 feet.

There are a number of important factors relating to the concentration of insects. Temperature appears most important, the optimum being between 75-80° F. There is a rapid decrease with temperatures over 90° F or under 70° F. Concentration increases with a rise in absolute humidity; the optimum dew point being 62° F. Barometric pressure has variable effects; in some instances, a lowering pressure causes activity and swarming at higher altitudes, in others, a reverse effect. Wind velocity is a complex factor. For example, moths migrate with prevailing winds that are favorable. High wind velocities at lower levels appear to be of minor importance. Convection currents and other upward air streams carry large numbers of insects to high altitudes, even 15,000 feet, where wind velocities may be 100 to 200 miles per hour. Thus, passive migration may carry an aerial plankton thousands of miles from its origin.

Lack of conformity of insect-sensitive patients to race (Oriental, Caucasian) and region is further evidence of the universal distribution of the Hexopoda.

Temperature, winds and moisture affect the growth of the insect as well as the vegetation on which it feeds. These factors are partly con-

trolled by the geography of an area, such as mountains, valleys, swamps, lakes and rivers. For example, the temperature, winds and geography of the Great Lakes area are particularly suitable for the Caddis fly and Sand fly.

This paper will be concerned primarily with the stinging insects, mostly Hymenoptera. Since most patients can seldom identify the insect, it is of some value to know a little about the area where it is found, or perhaps the type of nest it makes. Most people are familiar with the honey bee hive, but are not familiar with the small nests which the bumble bee makes underground, so it might be of importance to know that the patient was stung while walking bare foot on garden grass.

The paper wasp *(Polistes pallipes)* is the largest, and builds small, open bottomed, comb type nests under eaves of barns and houses and in other open but protected places. It stings on provocation usually. The white faced hornet *(Vespa maculata)* builds the large, gray football-shaped nests which look like papier maché and are generally seen hanging from trees or shrubs. The white faced hornets need only the slightest threat to attack in large droves. The yellow jacket is the smallest of the three but probably the most frequent offender. Its nest is small, just under ground or on the ground near old logs. It is easily provoked and attacks promptly when accidentally encountered during planting or mowing. It may even build in the walls of houses.

Evelyn Rockwell, in 1952, did some interesting work on mosquito bite reactions and mosquito extracts. A. Brown, in 1938, reported an unusual case strongly suggesting the possibility of the Arthus phenomenon from mosquito bites. Some investigators reported on bedbugs, fleas and other insects.

It has long been known that the insect cuticle consists of protein, carbohydrates and sulfur containing materials. It was hoped that by studying the chemistry of the exoskeleton one might find which factors were allergenic.

The constituents of the exoskeleton of insects are Chitin, Arthropodin and Sclerotin. Chitin accounts for one-fourth to one-half dry weight of the cuticle. It is insoluble and does not react on skin tests. Arthropodin is a water-soluble protein accounting for 15 to 50 per cent of the cuticle and resembling sericin (silk gelatin). It is probably allergenic. It reacts on skin testing. Sclerotin is a water insoluble protein.

One must mention silk since it is produced by cells of ectodermal origin, although, strictly speaking, it is not part of the exoskeleton. It consists of 75 per cent fibroin and 25 per cent sericin. Silk is produced by many insects and may be one allergenic link between them.

Patients who are silk reactors may react to other insect antigens. Patients reacting to other insects may react to silk antigen. Reactions, large and immediate, may occur as often in atopic individuals as do reactions to other allergens.

The stinging mechanism in bees and wasps is an intricate one, but basically consists of an acid gland, a poison sac, an alkaline gland and a double hollow shaft. The venom is a mixture from both glands, generally acid in reaction, and is injected by means of the shaft, which may be barbed, as in the worker bee, so that the entire sac and shaft remains in the victim. However, the stinger of the queen bee, the bumble bee and the hornet has no barb so that the victim may be bitten repeatedly.

The nature of the venom is not yet clearly understood. It is known that venom's activity is destroyed by heat, oxidation and proteolytic enzymes. The formic acid is present in amounts too small to cause primary effects. The toxicity of the venom is not great enough to account for severe local or general reactions since bee keepers may have 50 to 100 stings per day with no ill effects. An eighteen-month-old child was stung 477 times in one day but survived following treatment with adrenalin and ACTH. However, a death was reported from 1200 stings at one time. The estimated amount of injected venom varies from 0.05 ml to 0.3 ml with 0.05 ml as the most likely amount.

The pharmacologic effects of venom were reported in 1922 by Phisalix, who suggested that the acid gland secreted the inflammatory and stupefying substances; the alkaline gland, the convulsant factor; and he also noted the presence of enzymes, specifically a hemolysin. In 1939, Kellaway reported on three active toxic components, a hemolysin, a neurotoxin causing edema and paralysis, and a histamine-like substance producing primary inflammation. In 1954, by means of paper chromatography, Jacques and Schacter demonstrated three highly active smooth muscle stimulants in wasp venom; one was histamine in very high concentration (16 mg/g), another was 5-hydroxytryptamine or serotonin (0.32 mg/g), and the third was called "Kinin," a substance resembling bradykinin, substance P, slow reacting substance and trypsin; all of these being polypeptides but all the properties of these are not identical to "Kinin."

"Kinin" can be boiled three to five minutes with no loss of activity for twenty-four to seventy-two hours. It can be frozen and kept for weeks at –10° C. It is heat stable in neutral or slightly acid solution but unstable at room temperature in aqueous or saline solution. It dialyses, but slowly. It is insoluble in 95 per cent alcohol or 95 per cent acetone or anhydrous ether. It is rapidly destroyed by crystalline trypsin or chymotrypsin. Its pharmalogic action causes a delayed slow contraction of isolated guinea pig and rabbit ileum and a marked lowering of arterial pressure in the rabbit but less marked in the cat.

When wasp and bee venom were investigated by means of paper chromatography, wasp venom was found to have histamine and 5-hydroxytryptamine, and Kinin was present as an eluate. Bee venom contained histamine, but no 5-hydroxytryptamine and no wasp "Kinin." Another substance in bee venom produced a delayed but rapidly desensitizing contraction of the ileum.

Studies by Neuman and Haberman in 1954, using ninhydrin in paper chromatography, showed seven consituents, two of which were proteic. Ninhydrin is a substance which when heated with protein yields a blue color. The reaction is due to amino acid groups in the protein molecule. Individual alpha amino acids give a positive protein test, the shade of color varying with the particular amino acid.

Separation of the proteic substances showed two fractions. Fraction I contains all the toxic properties previously ascribed to several different components. It was considered a true toxin and had no enzymatic action. It directly hemolyses washed red blood cells. It increases, after initial depression, the blood pressure of cats even after previous decapitation, adrenalectomy, atropine or antihistamine. It paralyses, after a brief excitation, the phrenic nerve of the rat and the isolated perfused superior cervical ganglion of the cat and the guinea pig ileum. Locally, it increases the permeability of skin vessels. On the conjunctiva or when injected intracutaneously it causes local inflammation. It inhibits plasma cholinesterase and coagulates fibrinogen. Plasma hyaluronic acid and lecithin inhibit Fraction I.

Fraction II is considered pharmacologically inert and non-toxic. It contains hyaluronidase and phospholipase A, which splits lecithin to lysolecithin and inactivates structure-bound enzymes such as brain and lung thromboplastin. It inhibits the heat coagulation of egg yolk and clears diluted egg yolk.

This is of interest because Haas in 1946, and Hadidian in 1953, showed that "pro invasin I"—a proteolytic enzyme in snake venom—destroyed the inhibitory activity of normal serum against testicular hyaluronidase when the serum was exposed to its action prior to incubation with hyaluronidase.

Hyaluronidase is antagonized by an enzyme present in normal blood plasma which has been called anti-invasin I. An enzyme, pro-invasin I, destroys anti-invasin I. Another enzyme in plasma, anti-invasin II, destroys pro invasin I. Hyaluronidase is a diffusing substance, and as such may play a part in the rapid diffusion of venom.

Types of reactions to the venom are the immediate, of the atopic or anaphylactic type, and the delayed, which occurs from twenty-four hours to four to ten days later by a mechanism similar to serum sickness. A third reaction should be mentioned consisting of an unusual amount and duration of local swelling.

The symptoms can occur after the first sting and an incubation period. Symptoms of immediate reaction may occur in fifteen seconds to minutes. They are immediate constriction of throat and chest; dyspnea, asthma, cyanosis; abdominal cramps, diarrhea, nausea, vomiting, chills, fever, vertigo; laryngeal strider; shock, coma, involuntary defecation or urination; bloody, frothy sputum, followed by slow recovery or death.

The delayed reaction consists of generalized urticaria, also Sonck papular urticaria; marked regional adenopathy; petechial hemorrhages, local, gen-

eralized, subcutaneous, in the specific organs and even the central nervous system.

Mueller in 1959 classified the clinical severity of the sting reactions as follows:

Slight General Reaction: Generalized urticaria, itching, malaise, anxiety
General Reaction: Any of above plus any two or more of the following: generalized edema, constricted feeling in chest, wheezing, abdominal pain, nausea and/or vomiting, dizziness
Severe General Reaction: Any of above plus any two or more of the following: dyspnea, dysphagia, hoarseness or thickened speech, marked weakness, confusion, feeling of impending disaster
Shock Reaction: Any of above plus any two or more of the following: cyanosis, fall in blood pressure, collapse, incontinence, unconsciousness

Autopsy findings of ten cases as reported by Schenkin and Williams were as follows:

1. Pulmonary emphysema
2. Cerebral edema
3. Fatty metamorphosis of liver
4. Dilatation of heart
5. Epicardial hemorrhage
6. Cerebral intraventricular hemorrhage
7. Fluid blood
8. Congestion of nasal sinuses
9. Cutaneous petechiae
10. Cerebral petechiae
11. Meningeal hyperemia
12. Fatty degeneration of heart
13. Cardiac hypertrophy
14. Lobar pneumonia

In order to attempt proper treatment, considerable study has been done of the specificity of sensitization. Many attempts by various procedures have been made to determine which allergens are common to a number of insects and which are specific for a single insect.

By means of intracutaneous tests, conjunctival tests and passive transference studies before and after absorption with a positive yellow jacket serum using the five Hymenoptera venoms, Loveless and Fackler, in 1956, drew up some interesting conclusions:

1. All the venom contained some antigen in common.
2. Cross test data suggests that not only common but type specific allergens, peculiar to the individual Hymenoptera, are involved.
3. All the active constituents of the *Vespa maculiformis* (YJ) venom were present in the venoms of the paper wasp and honey bee.
4. There was evidence for the absence in the bumble bee venom of the major activity in the wasp venom, indicating that the two venoms had much less in common than was the case for the rest of the Hymenoptera.
5. Both bumble bee and honey bee venoms had a different antigenic activity from the yellow jacket venom.

Bumble bee venom appeared to be lacking in important activities possessed by all the other Hymenoptera and had an important activity which was lacking in wasp venoms. It also possesses some minor activity which is lacking in the honey bee products whereas its major activity rests on a common component.

In January 1958, Foubert and Stier published a paper using another technique to determine the allergenic components of the most common stinging insects. They used the Ouchterlony type gel diffusion plates; the antibody was from the serum of sensitized rabbits and the antigens were extracts of yellow jacket, yellow hornet, black hornet, wasp and honey bee. The gel diffusion studies indicate the bee, wasp, yellow hornet, black hornet and yellow jacket extracts contain from four to six antigenic fractions. Probably two of these are immunologically identical in all of these insects. However, the remaining two to four antigenic fractions are specifically characteristic of the individual insect species and are not shared with other species.

They also did anaphylactic shock studies with guinea pigs. Usually, the homologous antigen precipitated fatal shock in every sensitized guinea pig. Except for yellow-jacket-sensitized animals, heterologous antigens produced a greater incidence of survival from anaphylaxis. Yellow jacket antigen would seem to have the greatest ability to produce sensitization to other stinging insects. Bee antigen would appear to have the least ability to produce sensitivity to heterologous antigens. The closest relationship to bee antigen would seem to be wasp. Except for yellow jacket, all the insect antigens produced a less consistent sensitization to heterologous antigens.

Various patients have had reactions to bees, but none to wasp or hornet stings. The converse is also true, indicating that man may become sensitive to individual antigenic fractions to the complete or partial exclusion of others. Sensitization may be to antigens shared by all stinging insects, to antigens contained only in a single species, or to antigens of both groups. Therefore, unless positive identification can be made of the offending insect, Foubert and Stier feel it would be safer to use a combination of the common offenders such as honey bee, wasp, yellow jacket and hornet for immunization. Mary Loveless preferred only yellow jacket venom in order to avoid possible sensitization to the other unidentified insects.

In February 1958, Pruzansky, Feinberg, Schick and Feinberg presented another technique for testing specificity. They used hemagglutination and hemagglutination inhibition studies as well as the gel diffusion techniques for comparison. They chose to use Mayfly, fly, cricket, cockroach and silk pupa for their extracts because of demonstrable whealing and clinical allergy in man as well as the availability of adequate quantities of a pure breed of insect. There is also a close taxonomic relationship between some forms and a distant biologic relationship between others.

The extracts were made of dried insect powder (1 gm:10 cc saline). The antisera were from immunized rabbits. By hemagglutination, extensive cross reactions occurred when the agglutination titer of each serum was determined against sheep cells coated with each extract.

Inhibition of agglutination in the five homologous systems of extract-coated cells and corresponding serum was appreciable only with homologous

extract, indicating that antigens of major quantitative significance are specific for each extract since only the homologous extract could effectively inhibit a homologous reaction. The cross reactions obtained between coated cells and heterologous serum show that at least some of the extracts contain similar or identical antigens in addition to major specific antigens.

Although the gel diffusion studies apparently confirmed the extensive cross reactions, it was found that normal rabbit serum produced the same patterns as anti-insect rabbit serum. Therefore, the gel diffusion studies could not be said either to confirm or negate the results obtained by hemagglutination.

Two possibilities are suggested: one, the observed bands of identity with normal serum are artifacts; and two, the bands may be specific reactions between heterogenic components of the insect extracts with some natural antibody present in rabbit serum.

It is of considerable interest that three groups of investigators adopting different techniques have reached essentially the same conclusions regarding the specificity of the insect antigens.

Since venom sensitivity is, in a sense, an artificially induced one similar to anaphylaxis, serum sickness or drug hypersensitivity, it would seem that any person, not necessarily atopic, could be sensitized.

However, Mueller, in 1959, indicated that skin sensitivity at higher dilutions occurred with much greater proportional frequency in the group with a history of other allergies than in the one without such history. Also, members of the allergic group are more likely to have severe sting reactions. It is also a fact that negative skin tests do not rule out hypersensitivity, nor does there appear to be an adequate explanation for the delayed tuberculin type reaction rather than an immediate wheal. Some patients without any other allergic history may have marked skin sensitivity to insect venoms and severe clinical reactions.

Skin testing thus becomes a matter of considerable concern. There are many different opinions and methods regarding skin testing and immunization. In 1956, Mary Loveless reported using pure venom of the offending insect where possible and making a pool of 10 to 100 sacs to avoid variation in the amount of venom per individual sac. This was made into serial dilutions; .01 ml was given intracutaneously, and .02 ml of the antigen was used for conjunctival tests, beginning with the strength of 0.1 sac/ .1 ml. If negative to the yellow jacket extract, used where the offending insect was unknown, the patient was considered not sensitive to the common Hymenoptera. If positive, further studies were made. For treatment of the unknown insect where other studies are not feasible, Loveless preferred yellow jacket extract alone since it contains the common antigens. For immunization, she chose the intracutaneous route during one visit, generally using six venom sacs. She challenged her patients with live insect stings and reported successful results. In 1960, Mary Loveless used the

repository method with a single injection and reports successful results as proved by challenge with the sting of the live insect.

Some investigators prefer scratch testing first; others deny its value. Mueller, in 1959, suggested the use of intracutaneous testing with insect extracts diluted from 1:100, up to 1:100 million, starting with the 1:100 million in doses of 0.02 ml to 0.03 ml each. If a positive reaction with a minimum erythema diameter of 2.0 cm occurs, no further testing is done. If no immediate reactions occurred in twenty minutes, the next lower dilution was applied.

Jerome Glaser prefers to test the patient intracutaneously with only the 1:100 million and the 1:10 million dilutions. If these are negative, the patient begins treatment with the 1:10 million solution of combined insect antigen, increasing gradually until tolerance or a maximum dose of 1.0 cc of the 1:100 dilution is reached. Injections may be given once or twice weekly and extended to intervals of two to four weeks later. Treatment should continue for at least three years. J. W. Thomas suggests that, if necessary, even daily treatment can be used until the dose reaches a maximum and then treatment can be spaced at intervals of every two to four weeks. As always, the medical acumen and experience of the allergist must be the deciding factors in determining the method of testing and the program of treatment.

The general consensus is that, in most cases, immunization is quite successful. However, all patients have not been followed long enough to ascertain how long immunity does last.

Last, but not least, emergency treatment for the sensitive individual must be carefully prescribed and outlined.

The patient can easily be taught to carry his treatment with him, even children as young as eight to ten years old. This is easier for boys and men because of the availability of pants pockets. Parents and other siblings can set up the emergency treatment in the glove compartment of a car, a special spot in a cottage or boat, or any easily accessible area.

Patients who have had reactions to insect stings are well aware of the possibility of fatal reactions and the need for rapid treatment. They and their families are quite likely to be cooperative. Fatal reactions generally occur within a matter of minutes so that it is of vital importance that emergency treatment be prompt.

One should immediately apply a tourniquet proximal to the area bitten. I prefer a long 1/2 inch rubber strip which could encircle a thigh as well as a smaller limb area. This is not large or bulky and can easily be carried in a pocket or purse. All patients carry Isuprel-Franol which is immediately placed under the tongue and an antihistamine which is swallowed as soon as the Isuprel dissolves, which is a matter of three to five minutes. We have taught our patients to carry a disposable sterile 1 cc syringe and hypo needle, and to keep with it a small rubber stoppered vial of adrenalin 1:1000 with instructions to inject one fourth to one half of the syringeful first

into any area they can reach, and another one fourth into the sting area. The tourniquet should be loosened for a brief period every ten minutes or so. All this assumes the patient has not had a shock reaction and is capable of carrying out the instructions or that some one similarly instructed is available to carry out the procedure.

Some allergists advise that the patient also be instructed to swallow four tablets of prednisone, 5 mg each, immediately after the sting, but prednisone does not become effective as rapidly as the Isuprel-Franol under the tongue.

If the patient goes into shock, the tourniquet, adrenalin and intramuscular or intravenous antihistamine—if available—can be life-saving. If the patient survives the first few minutes up to about one half hour, it may be possible in more severe cases to reach a physician or hospital where the customary methods of shock therapy can be instituted, including oxygen, intravenous Solu Cortef 100 mg (hydrocortisone) or ACTH 40 units intravenous in 5 per cent glucose solution, continuing the adrenalin 1:1000 and injectable antihistamine as indicated.

There is no doubt that many fatalities occur from insect bites which without any autopsy are ascribed to coronary disease or other diseases causing sudden death.

It is to be hoped that this paper, purposely kept in a rather general style, will serve to stimulate further interest in Insect Allergy.

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THE EXISTENCE of a peculiar idiosyncrasy, which makes certain individuals liable to catarrh and asthma from the presence of roses, appears to have been known from the middle of the sixteenth century. In the year 1565, Botallus (known to fame as the discoverer of the foramen ovale in the heart) affirmed that he knew persons who held the smell of roses in deadly hatred, because it gave rise to headache, sneezing, and troublesome itching of the nose. Somewhat later, Van Helmont mentions the odor of sweet-smelling substances as causing headache, and, in some cases, difficulty of breathing; he also gives the case of a canon who was "totâ aestate propemodum asthmaticus, totâque hyeme liber." It must be allowed, however, that this passage, though suggestive, is not quite conclusive as to the nature of the malady. In 1673 I. N. Binningerus says that he had often heard from James à Brun, a professor of the medical faculty in the University of Basle, that his wife, Ursula Falcisin (a lady, as he is careful to inform us, whose charms were of the "too, too solid" kind, "amph corporis et carnosi"), suffered from coryza for several weeks every year during the rose season.

A few years later we find Ledelius recounting the case of a merchant of Grünberg who could not smell a rose without immediately suffering from itching, followed by inflammation of the eyes, with profuse lachrymation and headache lasting some days. We come next to a case of especial interest, which was published in 1691 by J. Constant de Rebecque. The passage is important as conveying the result of an experienced physician's observation of his own symptoms. He tells us that for thirteen years he had been afflicted with coryza lasting throughout the rose season, and ceasing of itself when that time had passed ("per totum tempus quo rosae se mihi olfaciendas praebent durat, eoque elapso sponte desinit"). At first he attributed his sufferings to heat, but in the year 1685, when the summer was exceptionally hot and there were hardly any roses on account of caterpillars, he was struck by the fact that his annual disorder did not trouble him. The symptoms came on at once, however, on his inadvertently plucking a rose toward the end of the season. He concludes that something flows from roses ("e rosis aliquid effluere") which stings the nose (in his case exceptionally sensitive) and by means of tiny prickles produces a solution of continuity imperceptible to the sight ("aculeis quibusdam solutionem continui etsi non sensibus obviam excitat"). This observer,

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therefore, came very near the mark as to the real cause of the disease, to which he applied the term "coryza a rosarum odore."

An extraordinary case is related by Herlinus (on the authority of Adrian Spigelius, whose name still survives in one of the lobes of the liver) of a Roman cardinal, Oliver Caraffa, who could not bear the smell of roses. This is confirmed from personal knowledge by another writer, who adds that Caraffa was obliged every year to shut himself up during the rose season, guards being stationed at all the gates of his palace to stop any visitor who might be wearing or carrying the dreaded flower. It is, of course, possible that in this case the roses may have produced some other affection than rose fever; but, as it is distinctly stated that it was the smell to which the cardinal objected, we may, I think, fairly conclude that the "sting of the flesh" which tormented him was, in fact, rose-pollen.

About the end of the seventeenth century, Riedlin records the case of a merchant of his acquaintance who was afflicted with sneezing and catarrh every year when the roses were in bloom. Riedlin advised him to avoid the cause of his complaint, and modern science can suggest nothing better.

The case related by Hünerswolff of a man in whom the perfume of roses invariably produced an attack of coryza, had been often cited by modern writers. The celebrated Broussais appears to have been impeded in his botanical studies by a similar idiosyncrasy. Other cases have been reported in the earlier part of this work in illustration of the influence of idiosyncrasy.

The occasional influence of imagination in the production of hay fever has been referred to in dealing with that complaint, and a very remarkable case of rose cold has been reported by Dr. J. N. Mackenzie.

I have myself met with only one example of rose cold. The case was that of Mrs. N—, a lady, aged forty-two, living in Devonshire, who consulted me in 1864. She was very fond of roses, of which she had a large quantity in her garden. She had never found any inconvenience until three years previously, when she noticed that whenever she smelt *(sic)* a rose she was attacked with a severe sneezing, suffusion of the eyes, and headache, which lasted for some hours. After that, as far as possible, she kept roses at a distance, never had any cut or put into her rooms, and as she said, "was able to walk about the garden without being affected by the odor." The following year, however, she found that even in her garden, when the roses were in blossom, she was attacked by sneezing and running at the nose and eyes. She tried various remedies, but nothing gave her any relief. In 1864, after having suffered from the complaint for several weeks, she came up to town and consulted me. She was still suffering from nasal catarrh, but there seemed to be nothing the matter with her nose beyond severe congestion of the lining membrane, and a slight swelling of the turbinated bodies. I found Mrs. N— of a decidedly nervous temperament, and, though well nourished, rather weak. Her general health, however, was good, and she was not at all subject to

colds in the winter. She had not suffered from any illness since childhood, when she had the usual infantile complaints.

I recommended a nasal wash containing a little alum, and the patient rapidly got better; but I believe she would have done equally well without any treatment, as she always improved when she escaped from her roses. Mrs. N— returned home, had a bad attack, and then came back to London. After this I tried several remedies, both mechanical and medicinal, but they were only very partially successful, and this lady was obliged to banish roses altogether from her garden.

As the term rose cold still survives in America, though it is quite unknown in England, I published two or three years ago some of the historical examples which have been related in this article, and invited American physicians to send me any cases which had come under their own notice. The following typical instances have been selected out of a considerable number sent to me for publication:

AMERICAN CASES

No. 1.—Report by the Rev. Andrew Preston Peabody, D.D., LL.D., kindly forwarded by Dr. Farnham, Cambridge, Mass., October 2, 1884.

In my childhood and youth I was subject to what are called bad colds in the summer; but I had never heard of the rose cold, and cannot therefore identify those colds with the rose season. It may have been in 1833, perhaps as late as—no later than—1836, that I learned that there was such a disease as the rose cold. At that time there was very little culture of roses out of season. With me the cold commenced with the earliest blossoming of the small red rose, which was the first to make its appearance, and lasted through the rose season, leaving me in my usual health about the time that many of my friends began to suffer from what they called the hay cold (which, however, did not begin till the hay harvest was almost over). During this season (the rose season), there was great swelling of the nostrils and face, an oppressive sense of fullness in the head, an inflamed condition of the eyes, with frequent paroxysms of sneezing, and a discharge from the nose which made half a dozen pocket handkerchiefs a day no more than a normal supply. I found a relief in travelling in roseless regions, and remember once having enjoyed a day or two of entire relief on Cape Cod, to suffer with renewed severity on my landing at Boston. I was affected temporarily by roses out of season. I remember once in mid-winter, in calling on a sick parishioner, being seized with a violent paroxysm on the entrance into the room of the fiancé of the patient. My condition was such as to lead to the inquiry how long I had had so severe a cold. My reply was "Not five minutes; but I should think, did I not see to the contrary, that I was in a room full of roses." The young gentleman disappeared, and returned instantly with a huge bouquet of roses which, he said, finding that there was some one not of the family in the chamber, he had left in in the adjoining room. Both in and out of the rose season, I repeatedly had roses removed from churches where I preached, and I always detected their presence before I saw them.

The decline, and almost disappearance, of the disease in my case seem to me as remarkable as its existence. Since I came to Cambridge, in 1860, I have not suffered severely from it, though up to that time it had relaxed nothing of its severity. For the first few years of my residence here, roses were slightly annoying,

and during the rose season proper I suffered more than at other times from dust and cinders in the railway cars, and from the light through slatted blinds; but I now know no difference of seasons as to general health and comfort. A slight titillation of the nostrils certifies me of the beginning of the rose season; but, though habit makes me shy of handling roses, I do not suffer from having them about me whether within doors or out of doors. It seems to me that a change in my constitution can hardly have taken place so suddenly; but there was a great change in my habits of life. While I was a parish minister I had no vacations, and the commencement of summer found me wearied with my year's work and incapable of opposing the vis medicatrix of nature to any morbid influence. Here in Cambridge, before the written examination system was fully organized, there was a slackening of work toward the close of the term, and the near prospect of vacation made what work remained seem light. My theory is, that successive summers finding me in a better condition to encounter what had been my bane, there has been a gradual improvement of my constitution, and probably an alterative process to such a degree that precisely the same causes would not now produce the same effect.

If this statement can be of service to you, I am most happy to place it at your command.

No. 2.—Extract from a letter from Dr. Andrews, of Detroit, U.S.A., November 10, 1884.

Mrs. A.—, aet. forty-five, blonde, height 5 feet 5 inches, weight 130 pounds, of nervous temperament, a delicate but healthy person in every way; very rarely takes cold or has any bronchial affection; only has nasal catarrh in connection with the rose cold.

First noticed the peculiar susceptibility about fifteen years since, and then by accident. Undoubtedly she had been affected before, but had not connected the cause and effect. When once attention was called to the subject, found that the slightest exposure to rose perfume would bring on the symptoms; a single rose in a large room being sufficient to produce slight disturbance, which would soon pass off upon removal of the cause of irritation. Not only the fresh flowers, but the dried petals and also the attar, are obnoxious, thus proving that in this case, at least, pollen is not the exciting agent. The season of the year has no apparent influence; the presence of rose perfume at any time, and anywhere, is as sure to excite the catarrh as a spark is to explode gunpowder.

The perfume of violets, pansies, heliotrope, and tube rose have in a less degree the same effect, and very possibly other flowers. She is not at all subject to hay fever.

Two brothers have hay fever slightly, but not rose cold; one sister and the mother feel the effect of perfumes somewhat; three other sisters are exempt.

No. 3.—Extract from a letter from Dr. E. Sealy, Newark, N. J., August 30, 1884.

On the evening of June 2 of this year, I sat in my office reading, when a friend entered with a bouquet of beautiful roses which he had gathered from his garden, to present to me. The roses were freshly gathered and exquisitely fragrant. I held them in my hands for about half an hour, and at intervals of a few minutes buried my nose among them and fairly revelled in their perfume, and then laid them aside. About three-quarters of an hour afterward I experienced a sudden rise of fever,

with a sense of great heat in the head, and soon after noticed a feeling of dryness in the nostrils. Next morning I had a well-developed coryza, which continued several days.

I had never been a believer in rose cold, and had never thought the subject worthy of study; but the onset of this attack was so abruptly marked, and so closely related to the supposed cause, that my attention was very forcibly attracted. Even now I do not accept this as demonstrative evidence, but my former prejudices are shaken up, and I am on the alert for further facts.

No. 4—Extract from a letter from Dr. Bowie, San Francisco, September 19, 1884.

Miss R—, a young lady of nineteen years, is in the habit of visiting our county seat, where thousands upon thousands of roses grow. If she approaches the beds, an irresistible desire to sneeze comes over her. Should she pin a bunch of buds upon her breast, she not only sneezes, but has all the symptoms of a cold in the head—snuffing *(sic)*, headache, a feeling as though her nose was stopped up, and a slight watery discharge.

As an illustration of the truth of these things, I have examined her beforehand, and found everything perfect; and, upon allowing her to smell roses, have noticed all the conditions above, the mucous membrane becoming redder and appearing as though slightly swelled.

GERMAN CASES

Dr. Ziem, of Danzig, has met with two cases of rose cold, one of which he has described in detail.

The patient was a healthy man, aged twenty-eight, who consulted Dr. Ziem in Hamburg, at the end of June, 1883, on account of swelling of the eyelids, which was often so severe that he was scarcely able to open his eyes. The tumefaction, which gave rise to a disagreeable pressure on the eyes themselves, was seen to be due to oedema. On examining the nose, the turbinated bodies were found to be much swollen. The patient complained of a mucous secretion from the nose and pharynx, which he had suffered from for many years, and which originally came on in the month of June, soon after he had become assistant at a florist's, and recurring every year in the same month, lasted till the end of the autumn. He attributed the complaint to the inhalation of rose dust, and stated that he was always free from attacks in the winter and spring. Dr. Ziem treated the patient with electric cautery, but after applications had been used for six weeks, erysipelatous swelling of the face took place, which made it necessary to discontinue the treatment. The patient went into the country, and while there was entirely free from his trouble.

The master of the shop also suffered from severe cold in the head during the rose season, and for that reason never went near his business at that time of year.

The following has been reported as a case of artificial rose cold, by Dr. J. N. Mackenzie of Baltimore. It is, unfortunately, complicated by the fact of a number of other causes giving rise to the cold in addition to the artificial rose.

The patient was a stout lady, aged thirty-two, well nourished but physically weak, and of nervous temperament. She had been subject to sick headaches and neuralgia since she was grown up, and from infancy had suffered repeatedly from

coryza of unusual severity. Most of the members of her family were of nervous temperament; her aunt suffered from asthma, and her sister from periodic influenza.

The patient began to suffer from her present trouble when she was between six and eight years of age. The asthmatic feature of the case developed subsequently, the first attack appearing at the age of 12, and since then the disease had been growing progressively worse. Dr. J. N. Mackenzie observes as follows: The clinical history of this case is typical. About the latter part of May, or the first of June, the disease commenced as a coryza. For several days prior to its onset, she suffers from an indefinite sense of general depression, with a disagreeable feeling of heaviness in the head, which she in part attributes to the worry incident to expectation of the attack. The catarrhal symptoms may or may not be preceded by chilly sensations and general malaise. Their early or late appearance, seemingly, depends upon the condition of the atmosphere, as regards heat and moisture, and sudden and repeated fluctuations in the thermometer. A thunderstorm invariably brings on an attack, without regard to season. The catarrhal stage commences with profuse watery discharge from the nostrils, increased lachrymation with redness of the conjunctiva, itching of the puncta, and photophobia. To these are soon added oedematous swelling of the lids, chemosis, and disturbances of vision, which prevent the use of the eyes for reading, sewing, and the like. The nostrils become at once obstructed, the nose itches violently, and paroxysms of sneezing, lasting sometimes for an hour at a time, occur at frequent intervals. The exterior of the nose becomes intensely red, and toward the close of the stage the cuticle desquamates. There is nearly always present a short, hacking, dry, harassing cough, which is relieved by sternutation. With the obstruction of the nostrils, the severity of the symptoms is increased; there is an annoying tickling sensation in the throat, which the patient feels "she must tear out with her nails"; the voice becomes husky, nasal, and easily fatigued; the pharynx feels dry and full, the ears become "stopped up" and not unfrequently tinnitus forms a prominent symptom of the stage.

Her physician remarks that:

The paroxysms were excited by the following agencies: (1) A heated, sultry condition of the atmosphere; (2) sudden changes in the temperature; (3) dampness; (4) exposure to "night air"; (5) electrical disturbances of the atmosphere. She can foretell by her sensations the coming of a thunderstorm, and when the latter approaches, the attack is unusually violent, causing her to seek refuge in a closed apartment, when she inhales the fumes of an antispasmodic preparation until the storm is over; (6) exposure to a high wind; (7) sudden excitement; (8) fright; (9) physical overexertion; (10) worry; (11) overloading the stomach; during her disease she has the most voracious appetite, which she is irresistibly compelled to gratify, and in so doing generally brings on a paroxysm; (12) the inhalation of common dust, cinders, and gases, especially those given off in the combustion of coal; (13) the presence or odor of strong perfumes, as, for example, articles of the toilet, the smell of tobacco smoke—anything, in fine, that has a pronounced or penetrating and heavy odor, as the tube rose, lily, et cetera; (14) the presence or odor of hay and roses is especially active in exciting the attack. She cannot, for example, remain in a room where roses are kept, or wear them upon her person, without being seized with a violent paroxysm; nor can she come into close or remote contact with hay without the production of a similar result. Last summer, while on a visit to the country, she caught sight of a distant hayfield, when she was immediately seized with a coryza; and on several occasions while passing a haycart in the thoroughfares of the city was taken with an attack of asthma; (15) almost any stimulant, taken internally, such as brandy, whiskey, beer, etc.; (16) handling peaches; (17) the ingestion of fruit, quinia, and morphia.

ROSE COLD—MAC KENZIE

"The anterior segment of the nasal fossa" was highly sensitive, and the right inferior turbinated body was enormously hypertrophied. Dr. J. N. Mackenzie treated his patient with nerve-tonics, and used a soothing spray, while to the "most sensitive spots" in the nose, galvanic cautery was applied. The patient derived great benefit from the treatment, and in a fortnight considered that she had obtained permanent relief. The lady, however, still felt that if brought into contact with hay or roses she would have an attack, and therefore rigidly excluded the latter from her home. The doctor, who was skeptical as to the power of pollen to produce the paroxysm, after applying electric cautery, and when the patient had recovered from the immediate effects of this little operation, allowed the lady to see an artificial rose, which had previously been concealed. In a few minutes a severe attack of coryza came on, and was so severe that the doctor thought it advisable to hand the lady the artificial flower. A few days later the lady called again, "and on that occasion she buried her nostrils in a large fragrant specimen of the genuine article, and inhaled its pollen without the slightest tendency to the production of reflex acts."

This case is a very interesting one, and testifies to the skill of the physician who reported it. But I can scarcely accept it as a typical example of rose cold. I should consider a typical case, one in which the symptoms were produced by roses, and by no other cause.

Here seventeen causes are given, and under many of these seventeen it will be seen that a great many separate sources of the disease are included. Instead of seventeen, seventy might be made out, or perhaps seventy times seven. In fact, the case is one of a highly nervous person in whom an enormous variety of causes, both physical and mental, were capable of bringing on an attack of coryza. It would be interesting to know whether the cure has remained permanent, and whether it included invulnerability to the other causes (besides rose-pollen) of the complaint.

THE PATH OF LIFE

Each step requires an energy expenditure equivalent to over eleven pounds. Anyone marching for nine hours performs a quantity of work with which half a million briquettes could be raised from the floor to the height of a table. On the average, an individual takes twenty thousand steps daily; in eighty years the total would be about half a billion! If a person did not walk in various directions but always straight ahead, the path which he would traverse in the course of his lifetime would encircle the earth no less than six times; if we were to imagine a child running away from its mother into space, it would arrive at the moon as an old man just about ready to dig its grave among the extinct lunar craters.—FRITZ KAHN, *Man in Structure and Function*, New York, Alfred A. Knopf, 1953.

Progress in Allergy

PEDIATRIC ALLERGY

A Critical Review of the Literature

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(Continued from the February issue)

FOOD ALLERGY

A number of general review articles of food allergies in childhood, primarily from Europe, have appeared in the literature[497-501] No new methods of investigation or approaches to therapy of food allergy were presented in these reviews.

In one of the more stimulating articles which provided "food for thought" in regard to food allergy and intolerance, Pratt[502] discussed some of the dangers of manipulating diets in children and warned about uncritical diagnoses of food allergy. In this article the author discussed the definitions involved with problems of food allergy and intolerance and pointed out the importance of differentiating the two. In making this differentiation, he suggested that (1) all relevant factors should remain constant during administration—elimination and readministration of suspected allergens. (2) objective evidence be used as much as possible in assessing the untoward reaction, and "blind" and "placebo" factors always considered when subjective judgments are necessary, and (3) after a cause and effect relationship has been established, additional evidence should be sought before accepting allergy as the etiologic mechanism. In his discussion of immunologic and diagnostic features, he also pointed out that the literature is confusing in regard to the significance of "food tests" and that other tests—eosinophilia, radiologic studies, cytotoxic tests—have all proved inadequate. He attributed the difficulties involved in determining the frequency of allergic reactions to differing criteria used in making the diagnosis as well as the operation of multiple selection factors. He felt that dietary prophylactic measures in the newborn are not justified at the present time. Finally, he made a plea to avoid indiscriminate restrictions of food, and at the same time to recognize and remove foods to which the child has a real intolerance or allergy.

In an editorial comment on food allergy Kessler,[503] in general agreement with Pratt, emphasized the difficulty in proving that certain disorders and symptom complexes are the result of hypersensitivity reactions to foods. "To use food allergy as a scrap-basket diagnosis for a variety of problems, for which no other diagnosis has been found, is unsound and fails to add to our understanding of an important pediatric problem." (Because of the im-

portance of their message, both Pratt's and Kessler's articles should be read in their original form by all those who are interested in pediatric allergy.)

To determine the incidence and assess the role of food sensitivity in children with well-defined allergic disease, Freedman and Sellars[504] studied 150 children. Ninety-seven had atopic eczema, non-seasonal asthma or both. Of these, sixty-seven had a positive clinical food history or positive food tests. From observations over a period of three years, forty-seven of the sixty-seven "had proved food sensitivities" to a total of 121 foods. The manifestation of their food sensitivities was mostly unrelated to the asthma or eczema. Even when wheezing and eczema appeared to be due to food allergy, the authors had difficulty in proving this relationship. (Studies such as this serve to emphasize the need for further investigations of the basic mechanisms involved in food allergy and for well-controlled clinical studies to actually determine the importance of foods as etiologic factors of major allergic diseases.)

Although it is almost routine practice by pediatricians and pediatric allergists to withhold solids and particularly highly allergenic foods during the first few weeks of life, a recent report by the Academy of Pediatrics Committee on Nutrition on the feeding of solids to infants stated that the information available on normal full-term infants receiving solid foods in addition to cow's milk in the first few weeks of life has not thus far indicated an increase in allergic manifestations over infants fed cow's milk alone.[505] The Committee concluded that "further controlled observations are needed to determine whether it is justified to caution against the inclusion of the more allergenic foods such as wheat and egg white at an early age."

Because various types of corn sugars are used widely in infant feeding as carbohydrate modifiers of all types of milk formulas, Howard, Todd and Dalton[506] investigated five commonly used products for possible antigenic qualities by the passive transfer reaction and the Schultz-Dale test. From their data the authors concluded that there was suggestive evidence that detectable amounts of corn antigen or antigens may be present in certain sugars used in infant feedings. No evidence was presented to indicate that these amounts were sufficiently important; rather, it was suggested by the authors that additional work, both experimental and clinical, is indicated to clarify the role of corn as a possible allergen in infant feeding.

In similar type studies Todd *et al*[507] studied the relative antigenicity of raw egg yolk, hard-boiled egg yolk and a commercial variety of egg yolk (Gerber's®) used in infant feeding. These authors concluded that raw egg yolk has an antigenic capacity which is separate and distinct from that produced by egg white, although there is evidence of an additional antigen common to both. Sensitivity to egg yolk can be demonstrated only with raw egg yolk and commercial yolk showed antigenically significant amounts of egg white antigen in passive transfer studies, although appreciably less than those present in raw yolk. The commercial yolk used in their studies appeared to be non-antigenic with respect to egg yolk, egg white or a common antigen. The authors felt that these findings were further confirmation of the fact that heating of foods aids in their allergenic denaturation. However, they stressed that the utmost caution be exercised in the feeding of any preparation of egg yolk or egg white to an infant or child known or suspected of being sensitive to egg. (Although the authors were rightfully cautious in pointing out that animal experimentation and *in vitro* studies cannot always be applied to human beings, investigations of this nature are extremely helpful in presenting a clearer picture of the antigenic quality of

foods and allow the practitioner to have a point of embarcation for clinical studies in humans.)

Johnstone[508] incriminated rice intolerance as a frequent cause of increased hunger, colic, diarrhea, rhinorrhea, cough and wheezing in infants. He noted this form of rice intolerance in twenty-two of 157 infants with a positive family history for major allergic diseases; however, only two of seventy-five infants with a negative family history of allergy were intolerant to rice. The symptoms disappeared with the removal of rice from the infant's diet and returned with its reintroduction. On the basis of these findings, the author suggested that rice be omitted from routine elimination diets of infants suspected of food allergy. (The author in his discussion cautions against assuming that the symptoms observed were "truly allergic" in nature. The subsequent development of major respiratory allergies in eight of the twenty-three infants with the symptoms of "rice intolerance" is only presumptive evidence that the symptoms observed were allergic in origin.)

The allergenicity of honey in infant feeding was studied by Strem and Stoesser.[509] Based on their findings of fifty-two infants who were fed honey as a carbohydrate supplement in their formulas, these authors concluded that the incidence of allergic manifestations due to processed honey in infant feeding is unusually small.

Milk as an allergen has been the subject of several reviews as well as the object of several immunologic and clinical investigative studies.[510-522] Stanfield[511] in his review of the literature sought the answers to the following questions: (1) Can the disease due to allergy to cow's milk be defined? (2) How common is this disease and is milk a factor of importance in the so-called allergic diseases of infancy? (3) What are the best methods of treatment? In answer to the first question the author concluded that the condition of cow's milk allergy or sensitivity has thus far only been defined in a clinical form and that no definite correlation between clinical suspected cases and the experimental demonstration of an abnormal antigen-antibody response to cow's milk has been found. (Although it is true that many of the immunological studies correlate poorly with clinical sensitivity, this does not necessarily imply that an immunological mechanism is still not the basis of the reaction. In many of the well-recognized hypersensitivity reactions, antibodies cannot always be demonstrated by the techniques available at the present time. It is extremely likely as further information and techiques become available, that many of the mechanisms involved in "milk allergy" and other forms of allergic reactions will become clear.) In answer to the second question, the author gave the impression that cow's milk plays only a small part in allergic reactions. Finally, in answer to the question of treatment, he noted that desensitization was recommended as well as the use of milk substitutes.

Fries[512,513] in two separate articles also reviewed the subject of milk allergy in all its aspects. It was Fries' feelings that milk should be considered as a complex of antigens, at least eight different protein components having been identified by the newer techniques of protein separation. He was also of the opinion that the lactalbumin fraction may be made less allergenic by boiling or evaporation. Sensitization to the lactoglobulin and casein fractions usually calls for complete elimination of milk, as well as biologically related foods. The variable incidence of milk allergy as reported by various authors was discussed by Fries. He believed these variations were attributable to (1) the criteria used in making the diagnosis, (2) differences in the

age of the sample groups, (3) sampling influences based on the specialty of the reporting physician, and (4) lack of standardization and uniformity of materials and types of skin tests to milk. In his experience, milk allergy occurred in about 0.3 per cent of the allergic patients under his direct observation. (The reviewers have also noted about the same order of frequency in their own practice.)

Crawford, Kerrigan and Arnold[514] studied two infants acutely allergic to cow's milk. In both babies episodes of clinical deterioration, culminating in cyanotic, peripheral circulatory shock-like state, were repeatedly observed on exposure to cow's milk. Despite clinical evidence of a diminished circulatory volume, chloride space measurements suggesting an increase in extracellular fluid volume at the expense of intracellular fluid were associated with the allergic reaction. Balance data indicated that external losses of sodium and water were small and internal accumulations of potassium large. The authors felt that further experimental work was necessary for the elucidation of the responses observed in these infants. However, their studies indicated that allergy should be considered in the differential diagnosis in infants who show metabolic derangements which may superficially suggest primary renal or adrenal disease. Case reports of cow's milk allergy were also presented by Bower, Stanley-Roose and Wolff,[515] Davies,[516] and Caplin.[517]

Ratner and his colleagues[518-520] reported extensive experimental studies in the guinea pig with purified protein fractions of bovine milk. The purified protein fractions studied were alpha-casein, beta-lactoglobulin and alpha-lactalbumin. The method consisted of sensitizing guinea pigs and challenging them with the purified milk fractions. *In vitro* anaphylaxis (Schultz-Dale) experiments with isolated ileum were also carried out. The authors in their first series of experiments indicated that each protein fraction is immunologically homogeneous. Of the three fractions beta-lactoglobulin was the most antigenic while alpha-lactalbumin and alpha-casein were of a much lower order of antigenicity. Heretofore, lactalbumin had been considered the major protein in the production of milk allergy. In their second experiments a heat-denatured milk was shown to have lost the antigenicity of the alpha-lactalbumin fraction, partially lost that of the beta-lactoglobulin fraction and retained the antigenicity of the alpha-casein fraction. In their final series of studies, sensitization and challenge of the guinea pigs was carried out by the oral route. The results of these studies suggested to the authors that heat-denatured milk can be safely fed to individuals allergic to milk unless they are extraordinarily sensitive to the alpha-casein fraction which appeared to be more heat-stable. Saperstein[521] recently reported at the 16th Annual Congress of the American College of Allergy some experimental evidence on the antigenicity of milk that was contradictory to Ratner's *(et al)* observations. This author was able, after sensitizing guinea pigs with alpha- and beta-lactoglobulin, to shock them with evaporated milk by administering a ten-fold increase of antigenic dose over that used by Ratner. Thus, the Saperstein's findings suggest that heat-denatured milk may not be innocuous for patients sensitive to the alpha- and beta-lactoglobulin fractions. Kraybill *et al*[522] demonstrated the denaturing effects of heat processing, gamma radiation and ultraviolet radiation on the anaphylactogenic properties of milk in guinea pigs.

In early infancy the symptoms of galactosemia may easily be confused with those due to milk allergy. In reporting a case of galactosemia in an infant, Wilhelm[523] pointed out the similarity of symptoms characteristic of galactosemia and milk allergy and presented a table of the differential diag-

nostic points. In an editorial comment, Glaser[524] directed attention to two metabolic diseases which could be confused with allergy to cow's milk. First, the more commonly recognized and previously mentioned galactosemia, and the second, a rare, recently described familial hypoglycemia which is precipitated by the ingestion of the amino acid leucine.[525]

There has been some recent interest in passive immunity obtained through feeding milk containing antibodies produced by injecting an antigen into the udder, the so-called "diathelic immunization."[526,527] In calves this form of immunization appears to be a process in which the suckling calf injects organisms, natural to the oral cavity of the calf, through the teat into the cow's udder. These organisms then stimulate the mammary gland to produce antibody globulins which are secreted in milk and when ingested and absorbed in the blood, provide passive immunity at a time when the calf's immunomechanisms are immature and relatively incapable of response. Unfortunately, no evidence exists which indicates that protective passive immunity can be obtained in human infants by the ingestion of human colostrum or cow's milk containing immune globulins. The human newborn, in contrast to the dependent state of the calf for maternal colostrum antibodies, is independent of this need and, furthermore, appears incapable of absorbing antibody globulins in sufficient quantity to provide protective titers of antibodies in the blood.[528]

Milk substitutes, specifically the soya bean preparations, have been the object of several metabolic and clinical investigations.[529-531] Fomon[529] studied four infants, aged four to six and one-half months, for periods of thirty-eight to seventy-three days while receiving *ad libitum* feeding of a soya bean formula. No other source of calories was provided. The rate of weight gain in the infants was normal, and the nitrogen retention was comparable to normal full-term infants of similar ages fed human milk. Fomon concluded that soybean formula could be a valuable protein source for children in technically underdeveloped areas of the world where soya beans, but not animal proteins, are available.

In a study to ascertain the number of babies who accept a new soya bean milk preparation and to determine the incidence of reactions, Barnes[530] found that 83 per cent of 191 infants readily accepted the milk virtually without any reactions. In further metabolic experiments on this same milk substitute fed to four normal infants, Fomon and May[531] concluded that there appeared to be no great difference between this milk and human milk as a source of nourishment of small infants.

As evidence that stringent restrictions of the diet may lead to serious consequences, David and Wolf[532] presented a case of a five and one-half-month-old infant who died after a brief illness characterized by irritability, excessive sweating, abdominal distention, tachypnea, tachycardia and somnolence leading terminally to coma. At necropsy the infant was found to have pathologic findings compatible with both beriberi and Wernicke's encephalopathy. Investigation of the dietary history and analysis of the formula (Mull-Soy®) fed the patient confirmed the suspicion of deficient intake of vitamins. (The child was fed limited quantities of carrot, squash, sweet potato in addition to the Mull-Soy which was heated and kept in a thermos bottle, further destroying what little thiamine is present in this preparation. This case report should serve to emphasize the importance of vitamin supplementation of restricted diets used in the therapy of atopic dermatitis or other allergic conditions. Although it is common practice among pediatric allergists to supplement with only vitamins A, D and C, it would appear from this case just cited that it would be important to sup-

plement the diet with vitamins B_1 and probably others of the B-complex, particularly if the child must remain on the restricted diet for a prolonged period of time.)

Another example of the untoward effects of elimination diets has been the reported adverse effects of soya bean formulas on thyroid function in humans. Although the production of goiter in animals by the administration of soya bean preparations has been known for many years, with the exception of Rawson and Rall's[533] case report, this relationship had not been observed or recognized in humans. However, recently Van Wyk, Arnold, Wynn and Pepper[534] reported the case of a ten-month-old infant reared on a soybean product (Mull-Soy, Rx) from birth who developed a goiter and hypothyroidism which was cured by the administration of four drops of Lugol's solution and the replacement of the soybean product by cow's milk. The authors concluded from their extensive metabolic studies of the infant and of normal adult subjects that a goitrogenic agent was present in this particular soybean product, which interfered with thyroid hormone synthesis in susceptible individuals and which raised the daily requirements for iodine.

Shepard[535] has also observed three euthyroid children with enlargement of the thyroid, apparently related to the intake of a soybean milk (Mull-Soy, Rx). In two separate letters, Anderson and Howard[536] of the Borden Company and Sarett[537] of Mead Johnson & Co. related some of their own experimental studies on the development of goiter with the feeding of soya bean preparations and speculated on the possible etiologic mechanisms involved.

Another unusual syndrome possibly related to the ingestion of a soya bean milk was reported by Fleisher, DiGeorge and Huange.[538] These authors described three infants who, owing to episodes of diarrhea or "colic," received a soybean milk preparation. Severe hypoproteinemia was present in each of the patients and none exhibited significant proteinuria. The clinical course was characterized by temporary improvement followed by sudden deterioration and death in each case at four months of age. Postmortem examination confirmed the diagnosis of fibrocystic disease of the pancreas in all three infants. In one of the infants, substitution of a low-sodium whole cow's milk formula resulted in elevation of the serum proteins and disappearance of the edema. When soybean milk formula was reintroduced, edema and hypoproteinemia recurred only to disappear again when an evaporated cow's milk formula was given. The authors discussed the possible relationship of soybean feedings to the development of the syndrome and the importance of recognition of severe hypoproteinemia as an early manifestation of fibrocystic disease.

Vitamins occasionally have been shown to cause allergic reactions in man. Although approximately 200 cases of allergic or toxic reactions to thiamine have been reported in humans, Fahlberg and Dukes[539] were unable to induce hypersensitivity to this vitamin in guinea pigs. In answer to a question on allergy to ascorbic acid, a consultant stated that he has never seen a reaction to this vitamin.[540] (The reviewers have similarly never seen an allergic reaction to ascorbic acid and, surprisingly, have never been able to definitely document a hypersensitivity reaction to the fish-liver oils.) In studying various types of fish-liver oils for traces of fish by the gel diffusion technique, Cohen and Saba[541] found that there were wide variations in the components existing among the different lots of these materials. The fact that only trace amounts of fish protein were demonstrated in some lots of cod-liver and halibut oils would help to interpret the clinical observation that instances of fish-oil allergy apparently occur only in exquisitely fish-sensitive persons

and that the average fish-sensitive patient may well tolerate fish oils in the average small doses.

ALLERGY OF THE NERVOUS SYSTEM

Aird[542] summarized the present state of knowledge in regard to the possible allergic conditions affecting the central nervous system. He pointed out that although the evidence is highly suggestive that the perivenous demyelination associated with acute encephalomyelitis following virus infections and vaccination may be the same as the allergic encephalomyelitis produced experimentally, final proof for this thesis is lacking. He also felt there is insufficient conclusive evidence that the Guillain-Barre syndrome, Landry's paralysis and multiple sclerosis are of an allergic origin. The evidence that allergy is responsible for migraine, in his opinion, is even less clear since it would appear that the basic mechanism underlying this form of headache may be effectively stimulated by a number of nonspecific factors, among which allergy may be but one.

An excellent review of the current concepts of allergic encephalomyelitis was also presented in an editorial in the *British Medical Journal*.[543] It was concluded that the present state of our knowledge of allergic encephalitis is still unsatisfactory.

Bailey[544] and Greene,[545] in review articles, discussed the common causes and medical management of migraine headaches. Bickerstaff[546] reported thirty cases of periodic migrainous neuralgia (erythromyalgia of the head, histamine cephalgia, greater superficial petrosal neuralgia, cluster headaches, autonomic facial cephalgia). He believed this poorly recognized syndrome is well documented and related to the familiar migraine. It is characterized by paroxysmal unilateral facial and orbital pain accompanied by autonomic disturbances, arising with clock-work regularity, usually at night, and in bouts lasting several weeks, with spontaneous cessation. Ergotamine tartrate was his treatment of choice, and histamine desensitization and antihistamines were unsuccessful in his hands.

Prichard[547] studied nineteen children with abdominal pain of presumed cerebral origin and divided them into two clinical groups, one which he called abdominal migraine and the other abdominal epilepsy. In differentiating these two types of abdominal pain he felt it was important to note the mode of onset of sensory phenomena. In migraine the onset is gradual and progresses over a period of many minutes or longer whereas in epilepsy the symptoms are characteristically abrupt. Other differentiating points were a positive family history of migraine and a normal electroencephalogram in abdominal migraine in contrast to a negative family history of migraine and evidence of discharge in the temporal region of the electroencephalogram in children with abdominal epilepsy.

Hayden and Grossman[548] reported for the first time an interesting familial syndrome characterized by rectal, ocular and submaxiliary pain and flushing. The authors postulated that the syndrome represented a disturbance of the autonomic nervous system with somatic pain radiation and likened it to migraine, Horton's headache, causalgia or erythromelalgia.

Speer[549] reviewed the historical development of the concept of allergy as the underlying cause of some diseases of the nervous system. The diseases discussed included allergic convulsions, allergic headache, abnormal behavior patterns, and a group of miscellaneous conditions—allergic vertigo, multiple sclerosis, cyclic vomiting, and stammering. Speer attributed failure of neuroallergy to receive full recognition by the medical profession to three major factors: (1) overenthusiasm, (2) the rise of the psychogenic theory, and

(3) failure of skin test confirmation (the author might have added a fourth reason, namely, lack of good clear-cut experimental evidence in confirmation of the claims of an allergic etiology for some of the diseases mentioned). Both Speer[550] and Rowe[551] discussed the tension-fatigue syndrome which they attribute to hypersensitivity. Randolph[552] in addition described three children with myalgia which he attributed to the ingestion of various types of foods.

Some investigators in the past have noted either specific focal abnormalities or a high incidence of "abnormal" electro-encephalograms in allergic children. Berman *et al*[553] did twenty-five waking and sixteen sleeping *EEG* examinations in twenty-five children with major allergic diseases (asthma, atopic dermatitis or allergic rhinitis). In contrast to the earlier authors, Berman and his co-workers did not note occipital dysrhythmia as a prominent finding and in only two of the waking EEGs were any abnormalities noted. All of the tracings made during sleep were within normal limits. From their results they concluded that EEG changes occurred infrequently in allergic children.

Austen, Carmichael and Adams[554] reported three cases of a syndrome of headache, papilledema, impairment of consciousness and tremor and twitching of the extremities in association with symptoms and signs of pulmonary and cardiac decompensation. In a fourth patient papilledema was absent but the movement disorder was so marked that myoclonus was suspected. These authors considered the hypoxia and hypercapnia of pulmonary insufficiency primarily responsible for the production of the neurological syndrome. The therapeutic program that completely reversed the neurologic disturbance of three of the patients was directed toward restoration of cardiac and pulmonary compensation.

PSYCHIATRIC CONSIDERATIONS

Many different views of the psychosomatic aspects of allergy in children have been expressed by various authors. Some of these have already been mentioned in the section on atopic dermatitis and asthma. Rapaport's[555] experience with allergy in children has fortified his belief that allergic illnesses in childhood have a basic immunologic etiology. However, if after adequate treatment such illnesses fail to respond to medical management, he recommended that the child's physical and psychological environment be further evaluated. He also believed separation of the child from his usual surroundings, particularly his parents, for periods of six to twelve months gives results that are rewarding for the greater number of children.

Burgin[556] also found it difficult to accept the concept that some allergic patients react on a purely psychogenic basis. He called attention to the responses of some allergic children to emotional situations, which may be indistinguishable from those resulting from exposure to true allergens. He stressed the importance of recognizing that before any allergen or emotion can produce a response characteristic of allergic disease, the individual must be capable of reacting, *i.e.*, an atopic person.

Hinman[557] discussed the psychic manifestations observed in various allergic diseases (gastrointestinal allergy, asthma, and eczema) as well as the types of tensions which arise in the child and in the parents. He stressed that irrespective of whether the tensions are the cause or the result of the allergic disease, that they must be taken into account in the over-all management of the patient.

Miller and Baruch[558] presented their theories of the basic psychodynamics

in allergic children and again emphasized the role of maternal rejection as an important etiologic factor. These authors also presented a good many practical hints as to how to handle patients in the office so as to provide appropriate casual psychotherapy (as we all do knowingly or not).

Peshkin and Abramson[559] described their methods of management and the problems encountered in therapy sessions with parents of intractable asthmatic children. These authors were convinced from their experiences that group discussions were a helpful therapeutic procedure and that the data so obtained might be useful in delineating further knowledge of the basic psychological mechanisms involved.

Long *et al*[560] in an attempt to evaluate allergenic and psychogenic factors in eighteen allergic hospitalized children exposed them heavily with dust taken from the patient's own home. By the techniques used, they were unable to reproduce asthma in the children studied. In addition, both the mothers and children were studied by means of a battery of psychological tests, and by interviews of the children with psychiatrists and the mothers with social workers. The authors concluded that psychogenic factors were important in the production of asthma in children and that their evidence showed that the mother wished the child to remain infantile and dependent.

From personality studies of asthmatic children, their siblings, a group of congenital cardiacs and a group of normal controls, Neuhaus[561] concluded that chronically ill youngsters are more maladjusted and neurotic than well children. Because anxiety, insecurity and deep-seated maternal dependency were seen consistently among both groups of sick children, the author suggested that these factors be considered for evaluation and psychological treatment. In contrast to normal controls, well siblings of asthmatic and cardiac youngsters showed the same emotional patterns as did the sick children. This finding suggested (1) the sibling's personality patterns may be affected by the presence of a chronically ill child in the home, or (2) constitutional or familial factors contribute to the similar personality deviations in the sick and well children. While Neuhaus' report agrees with those of others investigating the personality of asthmatic children, it indicates that this personality pattern is not peculiar to asthmatics but rather to the chronically ill.

Since hyposensitization is an integral part of allergic therapy, Kassowitz's[562] report on the psychodynamic reaction of children to the use of hypodermic needles should be of interest to the allergist and pediatrician alike. During the first six months of life there appears to be an absence of apprehension, although reactions to the actual injection and following the injection were moderately pronounced. From the second half year of life up to and including the fourth year all reactions observed were intense with few exceptions. From four years of age onward, a steadily increasing percentage of children exhibited the outward signs of self-control, compliance and pride until at the age of nine to ten years, less than 20 per cent showed the earlier behavior pattern which ranged from slight reluctance to extreme fright. Kassowitz suggested that this ability to cope with painful but necessary experiences is an index of emotional maturity in the growing child.

A critical appraisal of psychosomatic factors in the field of dermatology was made by Maddin,[563] who pointed out some of the pitfalls of assuming that skin diseases are of psychogenic origin. Weiss[564] discussed the emotional factors in allergy with special reference to asthma and the methodological problems involved in their investigation.

DRUG REACTIONS

In a good general review article on the problem of drug reactions, Birt[565] pointed out that drug reactions have replaced syphilis as "the great imitator." The various mechanisms involved in the production of drug reactions were also listed. The author stressed that no tests are available which specifically diagnose hypersensitivity reactions to drugs and that patch tests are confirmatory evidence only in local contact reactions. The author warned against using drugs which are not strictly indicated and discouraged the use of potentially dangerous agents, particularly in self-limited diseases.

The emergency management of untoward reactions to drugs was discussed by Fisher.[566] He described his treatment for apnea, circulatory collapse, central nervous system stimulation and allergic reactions. The components of an emergency kit to combat these types of reactions were also listed.

Hemolytic reactions have long been recognized as complications to drug therapy. In recent years the mechanisms of some of these hemolytic reactions to drugs have been partially elucidated. A major contribution to this end has been the demonstration that an altered metabolism of the red cells in certain individuals, one defect being a deficiency of glucose-6-phosphate dehydrogenase enzyme, makes these subjects susceptible to hemolytic effects of certain drugs and chemicals: primaquine, phenacetin, sulfanilamides, naphthalene, Furadantin®, vitamin K analogues, and others. The metabolic defect of the red cells appears to be transmitted by a sex-linked gene and can be demonstrated by the glutathione stability test and by assaying for glucose-6-phosphate dehydrogenase. Comprehensive reviews of this subject have been presented by Beutler,[567] Zinkham and Lenhard,[568] Blattner[569,570] and others.[571]

That a deficiency of glucose-6-phosphate dehydrogenase activity in erythrocytes might also play a role in the hemolytic reactions observed after the ingestion of uncooked fava beans (favism) was reported by Zinkham, Lenhard and Child.[572] These authors reported studies performed on two Greek boys who developed severe hemolytic anemia after ingestion of uncooked fava beans. The three metabolic defects of red cells—diminished glutathione, a marked decrease in glutathione when whole blood is incubated with acetylphenylhydrazine, and a deficiency of glucose-6-phosphate dehydrogenase activity—were found in each patient and in certain members of each of the two families. They concluded that favism results from a metabolic defect in the red cells. The defect appears to be genetically determined. They also noted that the hemolytic anemia usually results only after the ingestion of uncooked fava beans because one of the subjects in the study with the red cell defects had eaten cooked fava beans all his life and had never had symptoms. Szeinberg, Asher and Sheba[573] have also noted a familial glutathione deficiency in erythrocytes of persons with a past history of favism, as well as in those individuals with hemolytic anemia due to drugs. Kantor and Arbesman[574] reported findings which suggested that an immunological mechanism might also play a role in the etiology of favism. These authors demonstrated anti-fava bean antibodies by means of hemagglutination in an untreated patient suffering from favism. However, patients with favism who had been treated by blood transfusions and recovered failed to show this type of antibody.

Shahidi and Diamond[575] described two cases of congenital nonspherocytic hemolytic anemia, both of whom showed the severe metabolic defects in erythrocytes described above. Because of the chronic hemolytic

process in these patients and the absence of exposure to drugs, the authors postulated that the erythrocyte deficient in glucose-6-phosphate dehydrogenase does not necessarily require the injurious effect of a drug to undergo hemolysis. On the basis of their findings, the authors suggested a reduced glutathione stability test and an assay of glucose-6-phosphate dehydrogenase be performed in all instances where the diagnosis of congenital nonspherocytic hemolytic anemia is made.

Todd and O'Donohoe[576] described an acute hemolytic reaction in a six-year-old child attributed to a recent infection with herpes simplex virus. Other hemolytic anemia reactions in children were described by Levy and Porgess[577] due to nitrofurantoin and by Hallowell[578] following the ingestion of para-dichlorobenzene. Two cases of chronic idiopathic autoimmune hemolytic anemia were also recorded by Larson.[579] Prednisone was found to be beneficial in most patients with symptomatic hemolytic anemia treated by Lightman *et al.*[580]

Barr, Kraepelien and Zetterstrom[581] described the clinical findings in two allergic children with acute hemolytic episodes in association with asthma, allergic rhinitis or eczema. The hemolytic reaction was found to be induced by the ingestion of minute amounts of foods or the inhalation of substances known to produce antigenic action in the sensitized individuals. It is interesting that in both cases the author described, the antigens which caused the allergic reaction (*i.e.*, asthma, allergic rhinitis or eczema) did not seem to produce the hemolytic reaction and vice versa.

Two fatal cases of thrombotic thrombocytopenic purpura with anemia were reported—one which was attributed to either an immunization with DPT or sulfonamide,[582] and the other thought to be due to para-aminosalicylic acid given for an apparent tuberculous infection.[583] Both of these children died from their apparent hypersensitivity reactions.

The general subject of toxic and allergic reactions to local anesthetics has been discussed by Green.[584] He described the various factors which influence general toxicity, the signs and symptoms of these reactions and advocated certain measures for the prevention and treatment of the untoward effects of these drugs. A consultant in answering a question submitted to the Queries and Minor Notes of the *J.A.M.A.* also presented an outline of the reactions observed following the injection of procaine hydrochloride.[585] Siegal,[586] in reporting three cases of repeated edema at the site of procaine anesthesia for minor dental procedures, described a skin testing technique which he considered valuable in determining this form of hypersensitivity to procaine. The test consisted of an intercutaneous injection of procaine, a positive reaction consisting of erythema and edema twenty-four hours later.

Fisher and Sturm[587] found that Xylocaine® was an excellent substitute for patients who had a procaine sensitivity and determined that this drug has no cross-reactivity with procaine. Simon, Beard and Willoughby[588] in a double-blind study using 2 per cent procaine and 1 per cent or 2 per cent tripelennamine for nerve block in ninety patients found these two drugs equally effective in producing local anesthesia. The authors suggested the use of tripelennamine in patients where doubt exists as to a patient's sensitivity to drugs of any kind and where there is an allergic background.

An unusual reaction to the local anesthetic of benzocaine was reported by Wolff[589] and also by Goluboff.[590] Both of these authors described cases of methemoglobulinemia following the local application of benzocaine ointments to the skin. (Because of the sensitizing properties of the "caine"

drugs, the reviewers have always avoided their use in the local treatment of any dermatologic disorder. Wolff's and Goluboff's reports emphasize the potential hazards of absorption of any agent applied to the skin and that caution and care should be exercised in selecting the type of medications used locally as well as those administered systemically.)

Although hypersensitivity reactions associated with sodium para-aminosalicylic therapy have been reported frequently in adults, their occurrence in children had not been noted until Matasaniotis, Jacobs and Smith[591] reported four cases of hypersensitivity to this drug. This hypersensitivity reaction consisted of elevation of temperature, a rash varying from urticarial to morbilliform in character, and those other symptoms previously described in adults. Agranulocytosis was the prominent feature in one of their patients and jaundice in another. Omission of the para-aminosalicylic acid caused the symptoms of hypersensitivity to subside. The authors stated that they could desensitize three of their patients to PAS by administering the drug after a period of three weeks' abstinence beginning with a dose of 5 mg and gradually increasing to the desired total daily dose. (Although desensitization proved to be beneficial in their patients, in general, desensitization to drugs is a dangerous procedure and is best avoided. The surest insurance against irreversible or even fatal effects is the prompt discontinuation of the drug and, if possible, substitution of an unrelated agent.)

Haber and Osborne[592] described two cases of icterus and fever related to the administration of isonicotinic acid hydrazine and reviewed the literature on the subject. The importance of recognizing fever and icterus as a toxic manifestation to this drug and para-aminosalicylic acid is stressed by these authors.

Although Ratner and Flynn,[593] on the basis of animal experiments in guinea pigs, concluded that piperazine is a non-allergenic drug, additional cases of hypersensitivity-like reactions continue to appear in the literature. Fine and Abram[594] reported two patients who had signs and symptoms that were consistent with the drug-induced serum sickness type of reaction. (Although the incidence and type of hypersensitivity that might develop from a drug will vary widely, all drugs should be considered as potential sensitizers and capable of producing toxic reactions if given in large enough quantities.)

Toxic reactions from the intramuscular injection of iron have been appearing with increasing frequency. Koszewski and Walsh[595] encountered skin rashes in two patients and an anaphylactoid reaction in one of eighteen treated with Imferon®. Shafer and Marlow[596] described a case of recurrent arthralgia and cellulitis in an adult, presumably secondary to intramuscular injections of iron-dextran combination and reviewed the literature of these types of reactions. [Because malignancy changes have been noted in the tissues of animals injected with iron-dextran (Imferon®), this product has been recently removed from the market.[597]]

A review of glutethimid (Doriden®) intoxication was presented by McBay and Katsas.[598] Several fatal cases allegedly due to poisoning with this drug were documented for the first time with autopsy and toxicologic analysis. The authors concluded from the study of the cases presented that the lethal dose of glutethimid for human patients is from 10 to 20 grams.

Nesbit[599] recorded the incidence of severe reactions from present-day urographic contrast materials noted by sixty-three members of the American Association of Genito-Urinary Surgeons. The opinion expressed by the majority of the urologists was that the antihistamines when combined with

the urographic contrast media were of distinct value in preventing serious reactions but were less useful in preventing lesser reactions such as nausea, vomiting and arm pain. The intradermal and conjunctival tests for sensitivity were considered to be of no value whereas the majority of the urologists believed that an injection of a test dose (1 cc of the medium) was a reliable method of detecting sensitivity.

ANTIMICROBIAL AGENTS

Paralleling the increasing number of available antimicrobial agents are the numerous reports of untoward side effects arising from their administration. Entire texts and many general review articles have been devoted to this subject, and it is not within the scope of this paper to review all these drugs nor to cite the many types of untoward reactions that have been observed.[600-606] Nevertheless, a few articles will be referred to that might be of interest to the pediatrician and allergist, and because most of the untoward effects observed from penicillin have been on a hypersensitivity basis, a more complete review of the literature pertaining to this drug will be presented.

A number of papers have been published on the untoward effects occurring with the administration of a recently introduced, long-acting sulfonamide, sulfamethoxypyridazine (Kynex®). Garner[607] described three cases of erythema multiform in children who developed Stevens-Johnson syndrome after the administration of excessive doses of this drug. In addition, cases of prolonged urticaria,[608] fixed drug eruptions and photosensitivity,[609] hypersensitivity myocarditis,[610] and hepatitis associated with fever and skin rashes have been reported with the use of this agent.[611]

Although neomycin is not ordinarily administered systemically, respiratory arrest has recently been described following its intraperitoneal use in surgical patients.[612,613] This drug, along with kanamycin and streptomycin, has also been shown to have some anticoagulant properties when present in high concentrations, which may be responsible for the development of local hematomas following its administration.[614]

Brunelle[615] recently reported a patient with severe renal impairment who became rapidly and profoundly deaf following the administration of kanamycin. Edwards and White[616] also warned against the use of streptomycin in patients who have some impairment of renal function and advised the use of the artificial kidney for oliguric patients who had been administered streptomycin. Loder and Walker[617] reported three cases of neuromuscular block occurring from the administration of streptomycin. A general review of the literature on drugs that are known to produce deafness was presented by Wehrs.[618]

A case report of a child who had a severe allergic reaction to novobiocin resembling the Stevens-Johnson syndrome was reported by Hughes.[619] A striking feature of the case was the involvement of the nervous system with nuchal rigidity, marked irritability, stupor, pleocytosis of the cerebrospinal fluid but negative bacterial and viral studies. In a query to the editors on the incidence of reactions to novobiocin, Aisenson[620] stated that he had noted skin reactions occurring in four of seven children who had received novobiocin sodium (Albamycin®). The consultant in answering the question pointed out that a transient skin rash is probably the commonest side effect observed from the administration of this drug. Although he indicated that novobiocin may be considered a relatively non-toxic drug which may be safely used with proper safeguards and indications, he did mention that

serious reactions to novobiocin, particularly leukopenia, may occur in about 1 per cent of the patients receiving this drug. Cox *et al*[621] observed a case of hepatitic dysfunction which was attributed to the administration of novobiocin.

Ristocetin therapy has been known to be associated with severe hematologic complications. Gangarosa, Landerman, Rosch and Herndon[622] reported these complications in eight of ten consecutive cases receiving ristocetin therapy, and they felt that thrombocytopenia as a result of this drug may have contributed to the death of two of these subjects. Newton and Ward[623] also reported two cases of leukopenia associated with the administration of this drug. Both groups of workers strongly suggested paying careful attention to the blood count in all patients receiving ristocetin. They further felt that its use should be limited to hospitalized patients where facilities for early recognition of complications would permit prompt therapy.

A rare complication of optic neuritis and atrophy was reported by Kass *et al*[624] from the administration of isoniazid. The administration of pyridoxine daily was advised to reduce the incidence of the neurotoxic effects. Mann[625] observed skin reactions and bronchospasm from the administration of isoniazid.

A review of allergic reactions to erythromycin was presented by Stryker, Sigel and Grolnick.[626] In administering this drug to 210 atopic patients, they observed no serious untoward effects.

In comparing the effects of the administration of tetracycline alone and of tetracycline combined with nystatin, Larkin and Heseltine[627] found that gastrointestinal side effects were noted much more frequently in patients treated with tetracycline alone. Ziprkowski and Glazer[628] reported a case of a maculo-papular eruption following the administration of tetracycline orally.

Although serious untoward effects on the hematopoietic system following the administration of chloramphenicol orally have been known for some time, it has been recently demonstrated by Sutherland[629] that other serious toxic manifestations may occur from this drug, particularly when administered in large doses to newborn infants. This author observed fatal cardiovascular collapse in three newborn infants who had received large doses of chloramphenicol for the treatment of staphylococcal infections. The absence of autopsy findings indicating any but minimal or subsiding infections in the three infants suggested to the author that their deaths resulted from an adverse drug reaction. (Since this original report has appeared, others throughout the country have made similar observations of unexplained deaths in newborn infants during chloramphenicol therapy, and it has been suggested by the manufacturer that when this drug is indicated no more than 25 mg per kilogram of body weight be administered to newborn infants.[630])

In subsequent studies Sutherland *et al*[631] determined that the acute lethal effect of chloramphenicol to the newborn animal is not limited to the human species. They found that a larger portion of chloramphenicol circulating in the blood is in an altered and inactive form in infants as compared to adult subjects. Their data suggested to the authors that more than one system may be responsible for the peculiar response of newborn infants to chloramphenicol. They also postulated that the elevated blood levels in infants, particularly in those whose deaths were otherwise poorly explained, were most likely related to poor excretion of conjugated chloramphenicol.

Of all the antibiotics presently available, penicillin appears to produce the

greatest number and severest reactions. In a survey covering a large number of general hospitals throughout this country, Welch *et al*[606] found 2,995 serious reactions from antibiotics, 1,070 of which were considered as "life threatening," with 106 deaths. Most of these serious reactions were anaphylactic in nature, and by far and away penicillin was the agent most frequently incriminated. This drug was also the most common cause of angioneurotic edema with involvement of the respiratory tract.

In another survey on the incidence of allergic reactions to penicillin in Australia, Andersen[632] found that reactions to penicillin occurred in eighty-eight subjects (1.3 per cent) of 6,832 patients who had received some form of parenteral penicillin. Of interest was the fact that these authors found that the male subjects reacted twice as commonly as the female.

As indicated in the aforementioned survey by Welch *et al*[606] one of the more serious complications observed from the administration of penicillin is the immediate type of anaphylactic reaction. As in the past, a great many reports of fatal and near fatal reactions have appeared in the literature[633-637] It has become increasingly clear that these serious reactions may occur from minute quantities administered by any of the routes in extremely sensitive individuals. For example, both Nystrom[638] and Gullat[639] reported patients who had severe anaphylactic reactions following placing a penicillin tablet or lozenge in the mouth. It was further demonstrated by Bernstein and Lustberg[640] that pre-treatment with steroids was not capable of inhibiting this form of anaphylaxis. These authors reported a patient who while receiving daily doses of prednisolone had an almost fatal anaphylactic reaction within thirty seconds after the intramuscular injection of penicillin.

Lewis[641] has advocated some preventative measures, which the reviewers believe worthy of repetition, to decrease the incidence of these severe immediate reactions to penicillin. (1) Topical application of penicillin in the form of cream, ointment, lozenges, chewing gum, aerosol, etc., should be abandoned. (2) Oral and parenteral administration should be held to cases in which there is a clear indication. (3) A detailed history should be made regarding previous reactions to drugs. (4) The use of scratch and intradermal skin tests for atopic individuals, for persons who have experienced previous reactions, and for those who have received much penicillin. (5) An interval of not more than ten days between individual injections in a course of therapy. (6) Patients who have suffered from an acute immediate reaction should be given a card that should be carried at all times. This author also outlined the measures that should be taken to treat an acute immediate reaction occurring from the administration of penicillin.

Other unusual reactions have been reported from the use of penicillin. Kastel[642] reported a case of gangrene in the foot of an infant after the administration of penicillin. This author speculated that the gangrene was secondary to the vasculitis from the administration of penicillin or procaine, or both. Breners[643] reported four cases of urticaria due to penicillin with allergic carditis. An apparently rare complication of hemorrhagic erythema multiforme bullosum accompanied by intestinal obstruction, all thought to be due to the administration of penicillin, was described by Bassett and Cole.[644]

A number of good papers have appeared on the reactions observed from the administration of benzathine penicillin. Krugman and Ebin[645] studied four different types of penicillin for intramuscular injection to compare their incidence of local reactions. The penicillins studied were (1) a suspension of benzathine penicillin G, 600,000 units in 1 ml; (2) benzathine penicillin G, 600,000 units with 5 mg of prednisolone in 1 ml; (3) benza-

thine penicillin G, 600,000 units in 2 ml; and (4) aqueous procaine penicillin, 1,200,000 units in 2 ml. Three hundred and twenty children were evaluated at twenty-four hours and the following percentages of severe local reactions were observed: with the first preparation, 54 per cent; with the second preparation, 9 per cent; with the third preparation, 11.5 per cent; and the fourth preparation, 4 per cent. The incidence of mild local reaction was the same for all four preparations.

Several other groups of workers have studied the untoward reactions to benzathine penicillin G used in the prophylaxis of streptococcal disease. Bernstein and Houser[646] studied the rate of sensitivity reactions to both single and repeated injections of benzathine penicillin. Serum sickness reactions occurred in 2 per cent of 614 men after one injection and in only one subject after 332 received a second injection. The rate of reaction to sterile saline solution was also studied in a group of subjects who served as controls. Maculopapular rashes, arthralgia, pruritus and feverishness occurred with equal frequency in the penicillin and saline controlled group. Serum sickness reactions, urticaria and pain at the site of injection, on the other hand, were observed more frequently with subjects receiving penicillin. Because of the high rate of reactions observed from the injection of 1,200,000 units of benzathine penicillin given in this study and because of previous reports showing lower reaction rates to smaller doses of benzathine penicillin, the authors suggested that a mass streptococcal prophylaxis program should use 600,000 to 900,000 units. Their findings were in contrast to McFarland's *et al*[647] study in which larger doses of benzathine penicillin produced a reaction rate comparable to the smaller doses. (The high incidence of reactions observed in Bernstein and Houser's control group should emphasize the importance of not attributing all signs and symptoms following an injection as hypersensitivity reactions.) In another mass prophylactic program, Schreir, Hockett and Seal[648] found an incidence of 0.74 per cent of sensitivity reactions following the administration of single 600,000 units of benzathine penicillin to 19,561 Navy recruits.

Sherwood *et al*[649] injected benzathine penicillin in doses of 600,000 units every four weeks and 900,000 units every six weeks and felt that it was a safe and feasible method of administering penicillin. On the other hand Hsu and Evans[650] observed one death and five other severe allergic reactions in thirty-two patients who had received benzathine penicillin in a prophylaxis program. These authors emphasized that the benefit of a penicillin prophylaxis program must be weighed against possible hazards which can occur from the administration of this drug.

Ström[651] in Sweden studied the reaction rate of four different penicillin preparations—penicillin G, penicillin G combined with probenecid, penicillin V, and penicillin V combined with probenecid—in the treatment of 390 children with streptococcal infection. Although no untoward reactions to penicillin G or penicillin V were observed, an overall reaction rate of 30.5 per cent was observed in those patients receiving the probenecid-penicillin preparation. Most of the side effects were of the delayed allergic type. One patient developed a severe bullous pseudomembranous type of reaction suggestive of a Stevens-Johnson syndrome. From his findings, the author cautioned against the use of probenecid-penicillin preparations, particularly when this drug was to be administered for prolonged periods.

As of the present time, there is no infallible method of predetermining whether a patient may have a serious reaction to penicillin, although most authorities are agreed that a skin test with penicillin may be helpful in

deciding which individuals are susceptible to immediate anaphylactic reactions. Smith[652] proposed a simplified procedure of testing for penicillin anaphylactic sensitivity consisting of the use of a drop of full-strength (300,000 units per milliliter) procaine penicillin solution to a skin scratch and into the conjunctival sac, and tested this procedure in 1,365 subjects. sixty-four of these patients had a history of previous sensitivity—forty-eight delayed urticaria, four serum sickness type, and twelve anaphylactic reactions. Of the twelve patients who had a history of previous anaphylactic reactions, all except two gave positive test responses. No helpful correlation was demonstrated between the immediate test responses and delayed penicillin reactions—urticaria and serum sickness. One of the patients who had a positive conjunctival test was later administered penicillin by another physician and died within five minutes after receiving the injection. It was also interesting to note that one of the subjects tested had a systemic reaction from the procedure outlined by Smith. (Others have reported severe anaphylactic reactions to minute quantities of penicillin during skin testing, and therefore the reviewers deem it advisable to use highly diluted penicillin in skin testing patients known to be sensitive to penicillin in order to avoid this potentially serious complication. One can always proceed to higher concentrations of penicillin if further testing is necessary. However, under no circumstances should a negative test of penicillin, irrespective of the concentration used in testing, be considered as ruling out all potential reactions to this agent. A history of previous reactions to penicillin still remains the most reliable criterion for identifying a patient sensitive to penicillin.)

Johnston and Cazort[653] similarly suggested the use of a skin test with penicillin before administering this drug to patients. Some of the pitfalls of this procedure were discussed by Gutmann[654] and by a consultant answering a question on the use of the penicillin skin test in *J.A.M.A.*[655]

Rajka and Vincze[656] claimed that by combining penicillin with gamma globulin it could be used as a diagnostic agent in the urticarial and serum sickness type reactions due to penicillin. In thirty-four of forty cases, positive intracutaneous tests were obtained with the combined testing agent as compared to sixteen with crystalline penicillin alone.

Other papers have appeared indicating that an antibody to penicillin has been demonstrated using the gel diffusion method and the hemagglutination technique.[657-659] (It still remains to be determined whether these tests will be helpful to the clinician in predetermining penicillin sensitivity.)

Davidson[660] reviewed the literature on the use of antihistamines with penicillin to decrease the incidence of reactions to this antibiotic and also reported the results of his own studies. He was of the opinion that the simultaneous administration of antihistamines prevented untoward effects from the administration of penicillin. On the other hand, Sciple, Knox and Montgomery,[661] in a controlled study of 4,537 patients, concluded that the addition of an antihistamine with the penicillin did not decrease the incidence of reactions.

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(To be continued in the April issue)

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Walter Modell, M.D., New York, N. Y., Clin. Pharmacol. Ther., 1:769 (Nov.-Dec.) 1960.

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Evidence for the existence of two corticotrophin-releasing factors, α and β.
A. V. Schally, R. N. Andersen, H. S. Lipscomb, J. M. Long and R. Guillemin. Nature, 188:1192 (Dec. 31) 1960.

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Allergy to flea bites. III. The experimental induction of flea bite sensitivity in guinea pigs by exposure to flea bites and by antigen prepared from whole flea extracts of *Ctenocephalides felis felis*
E. Benjamini, B. F. Feingold, and L. Kartman. Exp. Parasit., 10:214 (Oct.) 1960.

The relation of properdin and complement to the thermolabile cofactor of normal serum necessary for the reaction of specific antibody with influenza A2 virus.
A. D. Kociskova, B. Styk and L. Hana. Acta. Virol., 5:19 (Jan.) 1961.

News Items

AMERICAN HEART ASSOCIATION

The 1961 Annual Meeting and Scientific Sessions of the American Heart Association will be held in Bal Harbour, Miami Beach, Florida, October 20-24. The 34th Annual Scientific Sessions are scheduled from Friday, October 20, through Sunday, October 22, in the Americana Hotel.

May 15 has been set as the deadline for submitting abstracts of papers to be presented at the scientific sessions. Papers intended for presentation must be based on original investigations in, or related to, the cardiovascular field. Official forms for submitting abstracts may be obtained from Richard E. Hurley, M.D., Medical Associate, American Heart Association, 44 East 23rd Street, New York 10, New York.

PEDIATRIC POSTGRADUATE COURSE

A postgraduate course in pediatrics will be conducted by the University of Nebraska College of Medicine in cooperation with the Division of Maternal and Child Health, Nebraska State Department of Health, April 17 and 18, 1961. Program coordinators are Gordon E. Gibbs, M.D., and Donald C. Nilsson, M.D.

For further information, call or write: Postgraduate Affairs, University of Nebraska, College of Medicine, 42 and Dewey, Omaha 5, Nebraska.

SECTION OF ALLERGY, SOUTHERN MEDICAL ASSOCIATION

At a recent meeting of the Section of Allergy of the Southern Medical Association, the following officers were elected:

Chairman—Thomas E. Van Metre, Jr., M.D., Baltimore, Maryland
Vice Chairman—John P. McGovern, M.D., Houston, Texas
Secretary—Claude A. Frazier, M.D., Asheville, North Carolina.

The next meeting will be in Dallas, November 6, 1961.

THE NEW YORK ALLERGY SOCIETY

The next meeting of The New York Allergy Society will be held March 29, 1961, at Hotel Beekman Tower, 49th Street and First Avenue, New York City.

The program is as follows:

"Delayed Bacterial Allergy, Homograft Sensitivity and Autoimmune Disease—Expressions of the Immunologic Origins and Consequences of Individuality."

H. Sherwood Laurence, M.D., Associate Professor of Medicine, Head, Infectious Disease and Hypersensitivity Unit, New York University Medical Center.

Discussion: Merril Chase, Ph.D., Associate Professor, The Rockefeller Institute for Medical Research.

NEWS ITEMS

CUBAN SOCIETY OF ALLERGY

The Cuban Society of Allergy announces the election of the following officers for the term of 1961-1962:

President—Dr. José J. Pedrera
Vice President—Dr. Javier Fernández Castro
Secretary—Dr. Francisco de la Torre Madrazo
Treasurer—Dr. Armando Gómez Echevarria

PHILADELPHIA ALLERGY SOCIETY

The following are the newly elected officers for the year 1961 of the Philadelphia Allergy Society:

President—Dr. Leonard W. Parkhurst
Vice President—Dr. Sonia Stupniker
Secretary-Treasurer—Dr. Jay Spiegelman

ECUADOR SOCIETY OF ALLERGY

At a recent meeting of doctors from all over Ecuador, the Ecuador Society of Allergy was organized. The following officers were elected:

President—Dr. Plutarco Naranjo
Vice President—Dr. Enrique Uraga Peña
Secretary—Dr. Jorge Rodríguez
Treasurer—Dr. Rául Murgueytio

In Memoriam

TELL NELSON, M.D., F.A.C.A.

Dr. Tell Nelson of Honolulu, Hawaii, died November 18, 1960.

Dr. Nelson was born in New York, New York, in 1899. He received his B.S. degree from the University of Chicago in 1920. After graduation from Rush Medical College in 1923, he served his internship at Evanston Hospital, Evanston, Illinois. He was an instructor in pathology from 1924 to 1927 at the University of Chicago, where he was also associated with Dr. Karl Koessler in research in allergy. Dr. Nelson became associate in medicine (allergy) and director of the Allergy Clinic at the University of Illinois in 1929, and later received a master's degree in medicine from this institution. In 1930, he entered private practice in Evanston, and for several years was associated with Dr. Edward George Tatge. In 1941, he was called to active military duty, and served in the Pacific theater, where he attained the rank of Colonel, MC, AUS. After the war, he entered private practice in Honolulu.

Dr. Nelson was a charter member of the College and served on the Board of Regents in 1943-1944. He was also a Fellow of the American Academy of Allergy, The Chicago Allergy Society (President, 1938), the Chicago Institute of Medicine, American Therapeutic Society, American Association of Immunologists, A.A.A.S., Sigma Xi, The Association of Allergists for Mycological Investigations, Association of Military Surgeons, Honolulu County Medical Society, Hawaii Medical Association and the American Medical Association.

H.P.

Papers of Interest

Tondreau, R., Hodes, P, and Schmidt, E. R.: Joint infections following steroid therapy: roentgen manifestations. Am. J. Roentgenol., 82:258 (Aug.), 1959.
In sixteen of seventeen patients who had received corticosteroid hormones by intra-articular injections, infection occurred.

Meyer, J.: Dehydration therapy in dermatoses. Presse med., 67:722 (April 11), 1959 (In French).
A modified Kempner diet, mercurial diuretics and acetazolamide and the resulting dehydration are credited with good effects noted in twenty-eight patients suffering from urticaria, angio-edema, and varicose ulcers.

Batten, L.: Psychosomatic Disorders in children. Brit. M. J., 5129:1109 (April 25), 1959.
Allergy exists, psychosomatosis exists; but let us beware of applying the corresponding adjective to clinical pictures.

Smith, J., Jr., Engel, M., and Blank, H.: Triamcinolone in dermatologic therapy. J. Florida M. A., 46:960 (Feb.), 1960.
Of thirty-six eczematous and nine psoriatic patients who were treated with the title drug, the first group responded better.

Hoffman, F., Zimmerman, S., and Reese, J.: Fatal agranulocytosis associated with acetazolamide. New England J. Med., 262:242 (Feb. 4), 1960.
Third recorded case report. The patient was under treatment with bronchodilators, antibiotics and corticosteroid drugs.

Dixon, F., Kuhns, W., Weigle, W., and Taylor, P.: The lack of absorption of ingested bovine antibody in humans. Immunology, 83:437, 1959.
No absorption of diphtheria antitoxin in cow's serum, milk, or colostrum in high doses was observed in human adults and babies, even though a variety of highly sensitive methods of detection was used. This is of interest in view of recently published and publicized data suggesting the use of milk from cows treated with pollen for oral therapy of pollen allergies.

Salmon, E.: Immunoelectrophoretic study on antigens of human blood platelets, Schweiz. Med. Wochenschr., (Basel) 88:1047, 1958.
The platelets possess at least two antigens of their own. There are also antigens identical with those of the proteins of the blood plasma, namely albumin, fibrinogen, gamma globulin and macroglobulin.

Rodman, T., Karr, S., and Close, Henry P.: Radiation reaction in the lung. New England J. Med., 262:431 (Mar. 3), 1960.
Of interest because corticosteroid hormones caused great subjective improvement not confirmed by pulmonary function studies.

Hydovitz, J. D.: Occurrence of goiter in an infant on a soy diet. New England J. Med., 262:351 (Feb. 18), 1960.
In view of the prevalent use of soybean products as a substitute food in milk allergy, the implication of possible hypothyroid effect must be remembered.

Popper, H., and Schaffner, F.: Drug-induced hepatic injury. Ann. Int. Med., 51:1230 (Dec.), 1959.
Well documented review.

Maffia, A. J., Levbarg, M., Perillo, L. A., and Greenberg, W.: A new treatment of upper respiratory infections with trypsin-phenylephrine nose drops. Arch. Pediat., 77:28 (Jan.), 1960.
Of 202 children afflicted with upper respiratory tract infection or exacerbations of chronic sinusitis, there was excellent response in 175, with good results in twenty-three, and in four, a poor response.

BOOK REVIEWS

EXPERIMENTAL RESEARCHES ON HAY FEVER. By Charles H. Blackley. London: Dawson, 1959. Price $4.50.

This book had become so scarce that it was reprinted on the occasion of the 4th European Congress of Allergy held in London, 1959. How little our ideas of hay fever seem to have changed in a hundred years. Blackley's experiments leave no doubt that the cause of summer hay fever in England is due to grass pollen. He dislikes the idea that any associated asthma is due to spasm, but considers that all the symptoms could be explained by swelling of the mucosa. He mentions asthma due to animals, and he found that inhalation of penicillium spores caused hay fever-like symptoms. He admits that he knows of no remedy for hay fever and suggests that the only reasonable thing to do is to go to a place in the summer where there is little likelihood of much pollen.

Anyone at all interested in hay fever will wish to have a copy of this book now that it is available again. A.W.F.

HELP FOR YOUR HEADACHES. By Percy Brazil and William H. Green. New York: Arco Publishing Company, 1960. Price $2.88.

A technical writer and a neurologist have joined forces to produce a book of advice to the estimated thirteen million American sufferers of headache. This is, however, not a how-to-do-it hand book.

Allergists will find this a helpful reference book for their patients afflicted with migraine, sinus and histaminic headaches.

"An allergen," say the authors, "does not produce a headache directly but only by affecting those tissues which are capable of causing headache." In other words, migraine is a secondary effect from the histamine released by the allergic reaction. J.F.

PREJUDICES

Prejudices are never shaken by counterprejudices because we never perceive our prejudices to be such. We take them either for recent conclusions or for revealed truths, and the most serious prejudices of all, those that affect our thinking most, are generally below the level of consciousness. We think within the framework of concepts of which we are often unaware. Our most earnest thoughts are sometimes shaped by our absurdest delusions. We see what we want to see, and observation conforms to hypothesis. Thus it has been suggested that Darwin's theory of sexual selection was owing not to his observations as a naturalist, but to his convictions as a gentleman that certain courtesies were due a lady, although five minutes spent in watching chickens ought to have dispelled the assumption that nature shared its code.—BERGEN EVANS, *The Natural History of Nonsense,* Alfred A. Knopf, New York, 1946.

Books of Interest

BASIC OFFICE DERMATOLOGY. By Stuart Maddin, M.D., Julius L. Danto, and William D. Stewart, M.D. 308 pages. Springfield, Illinois: Charles C Thomas, 1960. Price, $11.75.

Skin disorders comprise an appreciable portion of a general physician's practice, averaging more than ten per cent of all his cases. However, this segment of his practice, if handled with reasonable diagnostic and therapeutic skill should not cause the physician the concern that we often find it now does.

The logical application of history, physical examination and laboratory aids to dermatological patients, will accomplish just as satisfactory results in this field as in others. This manual is designed to make the average physician more knowledgable in the management of the common dermatoses.

It is our intent that the book should be used in the following manner:

1. As a ready reference for diagnosis and for the effective treatment of the common dermatoses.
2. To obtain help in unfamiliar cases, a diagnosis may be made by reference to the section on Regional Dermatological Diagnosis.
3. For those cases in which there is a lack of therapeutic response, a section on expanded therapy is included.
4. As an illustrated guide to the performance of some common diagnostic dermatological procedures.
5. As a reference manual containing an integrated approach to the problem of associated medical and dermatological disease.

An effort has been made to emphasize a single effective therapeutic outline for each condition. Such an approach has the advantage of simplifying one segment of dermatology which can be confusing and misleading. However, in so approaching the problem of therapy we have of necessity omitted certain drugs and non-specific therapeutic aids, even though they may still enjoy wide use. Proprietary medications are used when possible because of their standardization and ease of obtainability.

Sections on Dermatologic Counselling, and Dermatologic Allergy, should fulfill a double purpose. In them the physician can gain information on some of the wider aspects of dermatology, and also get some answers to some questions that we find commonly asked by patients.

AUTHOR'S PREFACE.

Successful from point of view of drawings, black and white illustrations in color. Treatment methods are succinct and clear. Worth having. *(Editor's comment.)*

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